Glucose Tolerance in Hypertension and Obesity

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Interest in the glucose tolerance of patients with hypertension and obesity arose from an intensive study of a group of hypertensive obese patients who were suspected of suffering from the Cushing syndrome. Among a number of diagnostic procedures, blood chemical examinations, determinations of the basal metabolic rate and urinary neutral 17-hydroxy-ketosteroids together with X-ray examinations of the skull, spine and long bones did not disclose consistent abnormalities. However, a diminished glucose tolerance or "diabetic curve" was observed in a majority of these patients.

The relation between obesity and glucose tolerance on the one hand, and hypertension and glucose tolerance on the other hand, has been noted previously. In 1922, standard glucose tolerance tests were performed by Paullin and Sauls[1] on 26 male and female patients, and 15 of these, or 57.6 per cent showed a diminished glucose tolerance. In 1929 John[2] in a report on 1,100 glucose tolerance estimations found diabetic curves in 65.6 per cent of 79 male and 62.2 per cent of 93 female obese patients. In 1936 Joslin, Dublin and Marks[3] reported 3,094 patients with diabetes mellitus of whom 63 per cent of the males and 67 per cent of the females were obese. In 1939 Newburgh and Conn[4] found close to two-thirds of their diabetic patients from 30 to 65 years of age to be obese when treatment for diabetes was first begun. However, in 1942 Ray[5], in a group of 110 unselected obese patients on whom a glucose tolerance test was done, reported only 16 per cent diabetic curves in his female patients and 14 per cent in his male patients.

In 1939, Short and Johnson[6] performed glucose tolerance tests on 541 patients, 132 of whom were of normal weight and 409 of whom were overweight. They reported that there was unmistakable correlation between the degree of obesity and incidence of diminished glucose tolerance, irrespective of age. On the other hand, Ogilvie[7], in 1935, performed glucose tolerance tests on 65 obese subjects, all females except 2, and concluded that sugar tolerance diminishes as the duration of obesity increases, but that the sugar tolerance in the obese subject is not related to the amount of overweight.

The relationship between hypertension and diminished glucose tolerance was noted by O'Hare[8] in 1920. In 1932, John[9] reported that a close relationship exists between hypertension and diabetes, and that hypertension occurs more frequently in diabetics than in non-diabetics.

The frequent co-existence of hypertension, obesity and diminished glucose tolerance was noted by Herrick[10] in 1923, and by Musser and Wright[11] in 1933. They concluded that there is a definite syndrome of obesity, hypertension and hyperglycemia.

We felt that the subject of glucose tolerance in obesity and hypertension needed further study, in order to elucidate the effect of hypertension and obesity, separately and together, on the glucose tolerance.

METHODS AND MATERIALS

Three groups of patients have been studied during the past four years: (a) those with hypertension and obesity, (b) those with obesity without hypertension, and (c) those with hypertension without obesity. All patients were males, 20 to 73 years of age. All patients classified as obese were unmistakably overweight. However, for purposes of statistical correlation the ponderal index described by S. C. Robinson[12] was employed; this is obtained by dividing the weight in pounds by the height in inches. A ponderal index of 2 to 2.5 is normal. All the non-obese patients had a ponderal index below 2.5; and all the obese patients had a ponderal index above 2.7. The ponderal index was employed as a matter of convenience. However, the data were rechecked by percentage of overweight, using standard height and weight and age tables, and the results were similar to those obtained with the ponderal index. All the hypertensive patients had blood pressure readings above 150/90. Patients with known diabetes mellitus, liver diseases, hyperthyroidism or frank Cushing syndrome were eliminated from the study.

The standard one dose oral glucose tolerance test was employed in this work. One hundred grams of glucose

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were administered to all patients. Blood and urine were examined in the fasting state and ½, 1, 2, and 3-hour intervals after ingestion of glucose. The patients were on their accustomed unrestricted diet up to the morning of the test as suggested by Blotner[13]. The blood sugar was determined by the Folin-Wu method, using venous blood, with the exception of one patient (Case No. 60 Table II A) from whom venous blood was difficult to obtain because of extreme obesity. In this case, capillary blood was used. In three of the patients whose fasting blood sugar exceeded 150 mg. per 100 cc. the glucose tolerance test was not done. Two of these patients were in the hypertensive obese group, and one in the normotensive obese group.

There is difference of opinion about the criteria for the interpretation of the glucose tolerance test. Mosenthal[14] and Moyer and Womack[15] agree that the blood sugar two hours after the ingestion of glucose is the key figure of the data furnished by the test. These authors accept a blood glucose of 120 mg. per 100 cc. two hours after the administration of glucose as the upper limit of normal. However, a higher figure was arbitrarily adopted as the criterion in this study. A level of 135 to 149 was designated as slightly abnormal, and 150 and above, as grossly abnormal. These higher figures were chosen to minimize "false positive" and questionable tests.

RESULTS

Table 1 summarizes the results of this investigation:

Among 60 patients in the *hypertension with obesity* group, 43 had abnormal glucose tolerance tests with second-hour blood sugar values above 135. Of these, 38 were grossly abnormal with second-hour blood sugar values of 150 or over; 5 patients had slightly abnormal tests with second-hour blood sugar values of 135 to 150. Seventeen patients had second-hour blood sugar values below 135. There were 42 patients in the *obesity without hypertension* group; 19 showed abnormal glucose tolerance tests with second-hour blood sugar values above 135. Of these, 10 were grossly abnormal with second-hour blood sugar values of 150 or over; 9 patients had slightly abnormal tests with second-hour blood sugar values of 135 to 150. Twenty-three patients had second-hour blood sugar values below 135. There were 52 patients in the *hypertension without obesity* group; 19 patients showed abnormal glucose tolerance tests with second-hour blood sugar values above 135. Of these, 11 were grossly abnormal with second-hour blood sugar values of 150 or over; and 8 had slightly abnormal tests with second-hour blood sugar values of 135-150. Thirty-three patients had second-hour blood sugar values below 135. Glycosuria appeared during the glucose tolerance test in 26 patients in the hypertension and obesity group; in 12 patients in the obesity without hypertension group; and in 10 patients in the hypertension without obesity group.

TABLE 1

Glucose tolerance
in
1. *Hypertension and obesity*
2. *Obesity without hypertension*
3. *Hypertension without obesity*

	Hypertension and obesity	Obesity	Hypertension
Total Cases	60	42	52
Total Abnormal	43	19	19
Grossly Abnormal 2nd Hour 150 +	38	10	11
Slightly Abnormal 2nd Hour 135 +	5	9	8
Normal	17	23	33
Glycosuria During Test	26	12	10

The distribution of abnormal glucose tolerance tests in the three groups studied is shown in Figure 1. It is to be noted that there were almost three times as many grossly abnormal tests in the obesity with hypertension group as in either of the other two groups.

The age distribution of patients is demonstrated in Figure 2. On the whole, the ages of the patients are comparable in the three groups although the hypertension without obesity group is slightly older.

AGE AND WEIGHT TO GLUCOSE TOLERANCE

The relation of age to glucose tolerance is shown in Scatter Diagram No. 1. It is noted that the scatter is not indicative of any apparent trend, and that therefore no definite correlation between age and glucose tolerance is suggested.

The relation of the ponderal index to glucose tolerance is shown in Scatter Diagram No. 2. It reveals that in the range between ponderal indices 2.7 and 3.8, the latter indicated by a horizontal broken line, the scatter is fairly uniform, showing no apparent correlation between the glucose tolerance and the degree of obesity as shown by the ponderal index. However, there is a sharp increase in the incidence of abnormal glucose tolerance tests, when the ponderal index exceeds 3.8.

CHART I.

DISTRIBUTION OF ABNORMAL GLUCOSE TOLERANCE TESTS IN THE THREE GROUPS STUDIED

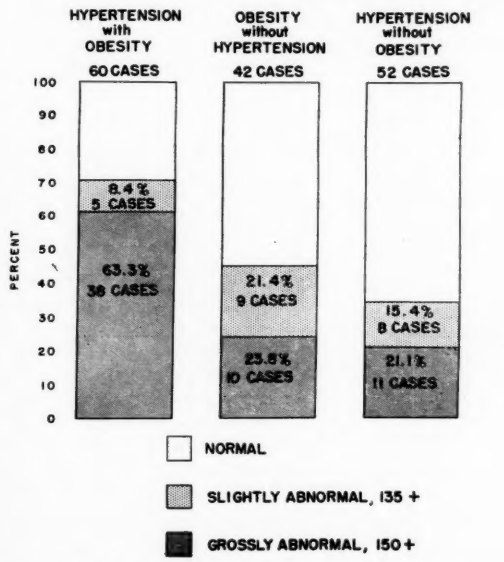


FIGURE I. Distribution of abnormal glucose tolerance tests in the three groups studied.

CHART II

AGE DISTRIBUTION OF PATIENTS

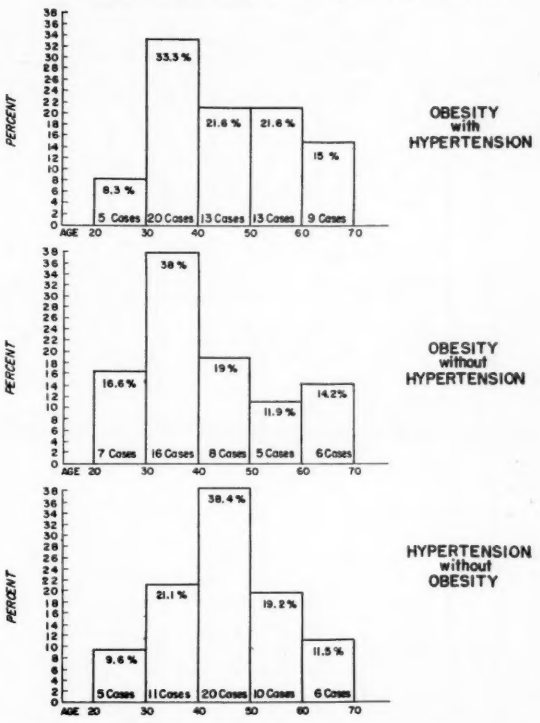


FIGURE II. Age distribution of patients in the three groups studied. It should be noted that the age distribution is similar in the two obese groups. The hypertension without obesity group is slightly older.

Tables 2 A, B, and C show the age, blood pressure, weight, height, ponderal index, glucose tolerance, blood sugar results, fasting ½ hour, 1 hour, 2 hours and 3 hours, and corresponding urine examinations for glucose in the three groups of patients.

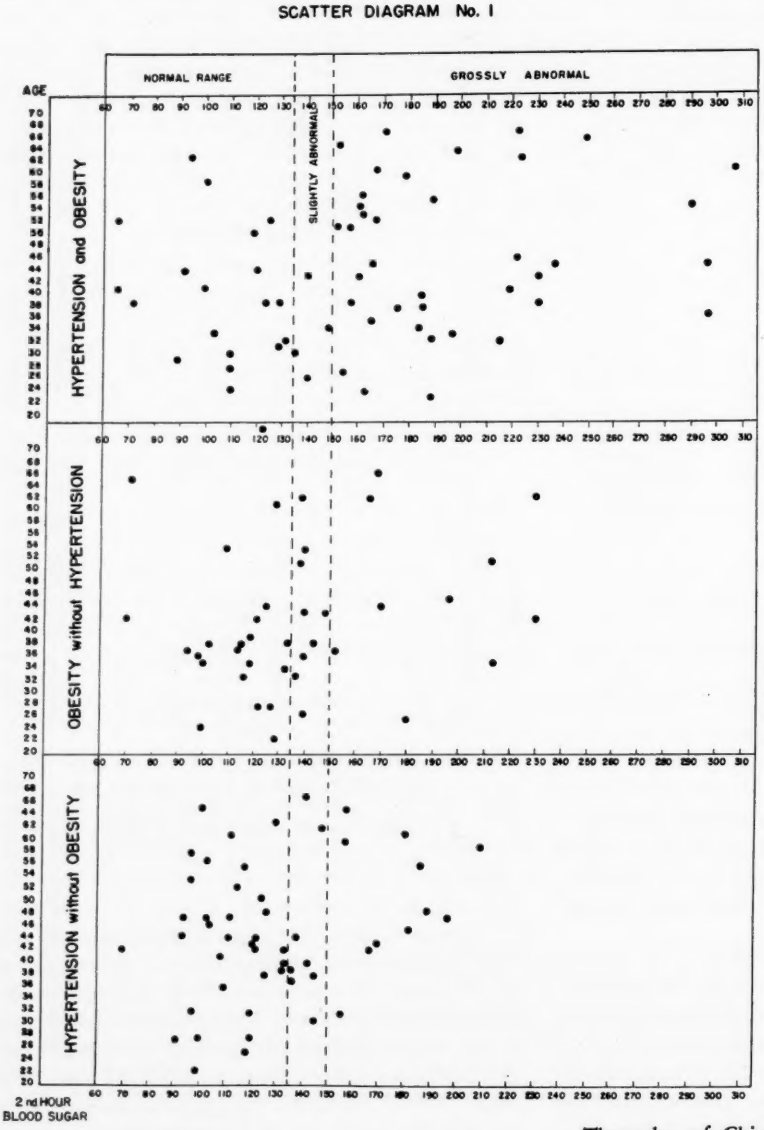
The relation of diastolic blood pressure to glucose tolerance in the two hypertensive groups is presented in Table 3, and the relation of systolic blood pressure to glucose tolerance in the two hypertensive groups is presented in Table 4. There is no apparent correlation between the height of blood pressure and the degree of abnormality of the glucose tolerance test.

COMMENT

The first observation emerging from this investigation is the high incidence of diminished glucose tolerance tests. This is all the more striking when one compares this high incidence with that reported in normal controls, and in the general population. Moyer and Womack[15] reported no diabetic curves in their group of 103 normal controls. In 1947, Wilkerson and Krall[16] reported an incidence of 1.7 per cent of diabetes in the general population based upon a study conducted under the auspices of the United States Public Health Service in the town of Oxford, Mass., where 70.6 per cent of the inhabitants had their urine and blood tested for sugar. Marks[17] estimated a maximum incidence of 2 per cent diminished glucose tolerance tests in the general population on the basis of the figures reported by Wilkerson and Krall[16].

GROUPS FROM DIFFERENT POPULATIONS

The hypothesis that our three patient groups were drawn from the same population with regard to glucose tolerance was tested by means of a Chi-square contingency analysis, based upon the following table:



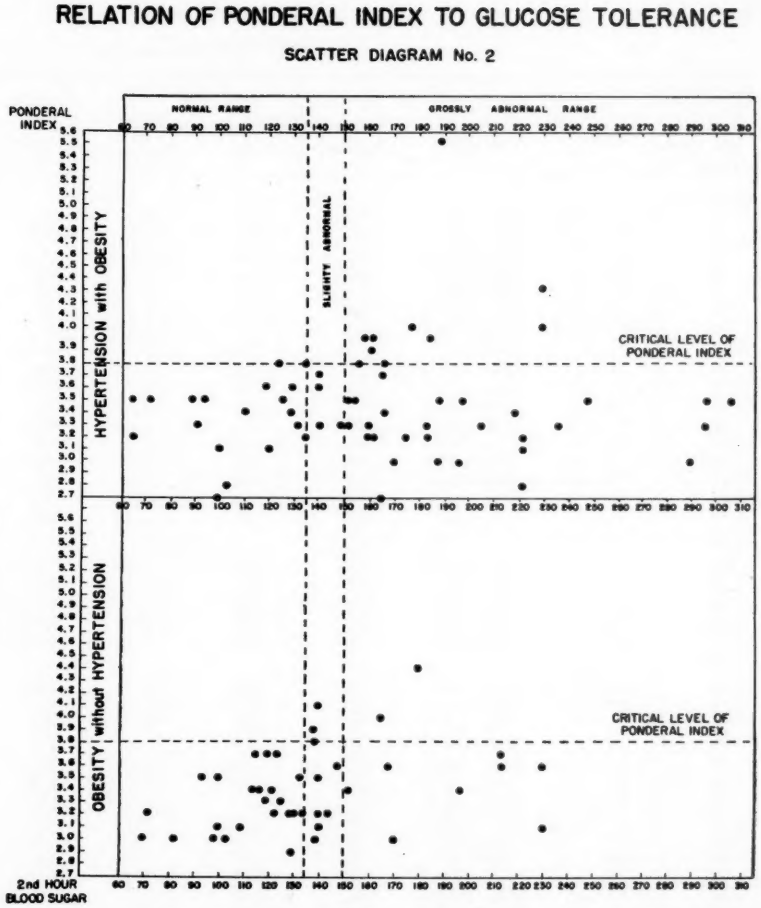
Relation of age to the glucose tolerance. The scatter is fairly uniform throughout and does not show any definite trend.

TABLE I (modified)

	Grossly Abnormal	*Slightly Abnormal*	*Normal*	*Total*
Hypertension with obesity (A)	38	5	17	60
Obesity without hypertension (B)	10	9	23	42
Hypertension without obesity (C)	11	8	33	52
		Grand Total		154

The value of Chi-square was 26.98, which, in this situation, (namely 4 degrees of freedom) would occur under the circumstances of the hypothesis less than one time in a thousand (P less than .001). Thus, we can reject this hypothesis with great confidence, and conclude that these diagnostic groups were not all drawn from the same population with regard to normality of glucose tolerance.

Analyzing these data further, it is possible to con-



Relation of the ponderal index to glucose tolerance in the two obese groups. The diagram shows that a ponderal index of 2.7 up to 3.8 has no definite correlation with the degree of abnormality of the glucose tolerance test. Above that value there is a sharp increase in the incidence of abnormal glucose tolerance tests.

clude that the A group gives a significantly higher incidence (P less than .001) of grossly abnormal tests than does either the B group or the C group; however, the B and C groups are similar in incidence (that is, the hypothesis that they were drawn from the same population with regard to abnormal incidence can *not* be rejected).

The incidence of abnormal tests in the general population is estimated at 2 per cent. All three of the groups under study give significantly (P less than .001) higher incidence than this.

This study also brings out the point that age does not have a demonstrable bearing upon the glucose tolerance. Short and Johnson[6] state that there is no definite relationship between age and the impairment of glucose tolerance. Blotner[18] came to a similar conclusion in 1945, when he studied 70 adult patients and 16 children, all of whom were confined to bed from one month to eight years, because of various diseases. Although all of these patients were nondiabetics, 63 of the adults and all of the children had diminished glucose tolerance curves. He attributed this finding to prolonged enforced rest and inactivity. Mosenthal[14] is also of the opinion that age *per se* does not influence the glucose tolerance, but that it is inactivity resultant from age which is responsible for the diminution of the tolerance for glucose. It may be that lessened activity is one of the factors responsible for the high incidence of diminished glucose tolerance tests among the patients studied here. Dublin and Marks[19] state that obese men and women have an aggregate mortality of 1½ times the expected normal. The study was based upon a group of 25,998 men and 24,901 women observed for 25 years or more. They also point out that a number of diseases are more

TABLE 2 A.

Hypertension and obesity

Second-Hour Blood Sugar mg. per 100cc. Case No.	Age	Blood Pressure	Height Inches	Weight Lbs.	Ponderal Index (WT/HT)	Glucose Tolerance					
						F	½	1	2	3	
Below 135											
1	41	140/100	70	228	3.2	78	109	119	65	52	
2	52	170/110	70	245	3.5	112	181	161	125	76	
3	44	170/110	74	236	3.1	110	190	175	120	110	
4	39	160/102	62	224	3.6	127	165	175	129	133	
5	41	200/140	71	193	2.7	96	171	161	99	102	
6	62	170/100	69	242	3.5	95	148	170	94	80	
7	39	160/130	64	247	3.8	127	177	194	124	90	
8	33	190/130	70	231	3.3	114	—	162	131	92	
9	34	210/130	69	198	2.8	110	159	163	103	64	
10	44	130/110	72	240	3.3	110	163	163	91	88	
11	39	170/120	70	247	3.5	92	163	163	72	66	
12	52	180/110	70	246	3.5	120	180	187	65	92	
13	58	170/110	69	215	3.1	98	193	168	100	100	*
14	30	190/95	75	266	3.5	115	148	90	89	103	
15	50	200/130	73	268	3.6	123	190	217	119	89	*
16	32	170/120	73	250	3.4	119	170	157	129	97.5	
17	31	170/120	67	228	3.4	106	145	166	110	100	
135 +											
18	27	150/120	68	245	3.6	120	180	195	140	120	*
19	31	150/106	72	230	3.2	123	190	165	135	103	*
20	27	180/90	70	265	3.8	111	159	150	135	92	
21	35	150/100	72	248	3.3	116	148	170	148	103	
22	43	150/100	70	234	3.3	106	170	148	140	88	
150 +											
23	36	150/100	71	264	3.7	100	141	234	165	116	
24	40	210/110	70	232	3.3	151	164	222	184	—	
25	25	148/100	70	283	4.0	85	—	182	162	—	
26	38	190/120	72	285	4.0	129	195	237	185	110	*
27	33	200/130	72	240	3.3	—	152	139	215	97.5	*
28	45	190/130	66	236	3.5	175	—	290	296	226	*
29	53	180/120	71	277	3.9	161	—	—	—	—	
30	43	170/110	66	274	4.1	103	237	296	230	230.5	*
31	37	160/110	69	232	3.3	140	238	290	296	200	*
32	39	160/120	71	282	4.0	106	185	195	157	115	*
33	54	170/90	70	225	3.2	160	—	—	—	—	
34	65	180/100	77	270	3.5	150	242	262	248	210	*
35	24	140/100	68	240	3.5	114	177	193	188	94	*
36	64	200/120	62	220	3.5	122	126	214	152	70	
37	34	170/100	68	206	3.0	148	190	250	196	115	
38	41	150/110	68	234	3.4	136	233	296	219	119	*
39	51	150/100	72	238	3.3	106	214	238	152	100	*
40	51	170/120	67	258	3.8	106	170	179	156	80	
41	43	150/100	64	212	3.3	136	165	184	160	136	
42	60	160/100	69	242	3.5	185	256	314	306	248	*
43	45	220/120	65	180	2.7	97	165	197	165	157	
44	66	180/100	72	214	3.0	110	180	208	170	89	
45	54	220/140	68	206	3.0	165	197	258	290	264	*
46	38	140/100	67	219	3.2	119	191	222	175	86	*
47	60	190/100	70	241	3.4	122	197	175	166	94	
48	45	180/110	68	225	3.3	122	—	298	236	85	*
49	59	178/98	66½	277	4.1	111	230	150	177	83	*
50	28	166/102	69	247	3.5	114	209	193	154	84	*
51	46	180/120	69	220	3.1	116	168	242	222	159	*
52	55	160/110	68	205	3.0	120	188	243	188	75	
53	35	160/110	68	224	3.2	133	266	244	184	108	*
54	66	160/110	68	195	2.8	127	187	187	222	163	
55	52	210/120	69	266	3.8	133	200	239	166	100	*
56	39	200/140	69	310	4.4	115	166	230	230	89	*
57	62	190/110	65	210	3.2	133	—	203	223	244	*
58	63	200/130	65	230	3.5	126	230	280	197	100	*
59	56	190/120	67	215	3.2	119	210	210	161	100	
60	33	170/130	64	360	5.6	127	188	193	188	109	

*=Glycosuria during test

TABLE 2 B.

Obesity without hypertension

Second-Hour Blood Sugar mg. per 100cc. Case No.	Age	Blood Pressure	Height Inches	Weight Lbs.	Ponderal Index (WT/HT)	Glucose Tolerance					
						F	½	1	2	3	
Below 135											
1	33	126/76	68	240	3.5	122	140	136	133	80	
2	34	124/76	67	236-43	3.5	115	170	165	100	119	*
3	43	106/78	63	210	3.3	116	157	125	125	86	
4	52	120/80	67	212	3.1	109	170	122	109	88	
5	20	110/70	70	212	3.0	94	126	119	82	91	
6	41	130/84	71	238	3.4	107	142	127	121	92	
7	41	110/80	68	200	3.0	110	142	168	70	123	
8	37	110/80	68	221	3.2	110	175	183	134	70	*
9	27	130/90	71	233	3.2	116	147	168	127	78	
10	36	110/78	63	216	3.4	114	172	198	114	98	
11	38	120/80	68	230	3.3	133	185	160	119	76	
12	24	130/80	68	218	3.1	106	129	106	100	70	
13	34	120/80	70	260	3.7	106	175	166	119	83	
14	73	116/80	66	215	3.2	137	208	192	123	149	
15	32	130/80	68	232	3.4	110	149	220	116	76	
16	27	140/86	70	265	3.7	120	161	165	123	97	*
17	59	100/80	70	206	2.9	116	133	141	129	106	
18	37	130/94	71	263	3.7	112	133	100	115	92	
19	63	110/80	68	223	3.2	105	154	142	71	84	
20	37	120/80	66	202	3.0	112	192	170	103	89	
21	22	110/80	68	222	3.2	103	175	175	129	72	
22	35	120/80	72	217	3.0	112	165	180	98	84	
23	36	122/75	67	237	3.5	109	118	122	94	86	
135+											
24	52	110/80	61	255	4.1	126	217	148	140	87	
25	42	120/80	71	260	3.6	207	219	248	148	100	*
26	35	120/80	66	207	3.1	115	184	196	140	115	*
27	26	120/80	70	248	3.5	115	185	201	140	73	
28	37	130/80	72	234	3.2	129	222	228	144	86	
29	60	110/70	67	201	3.0	117	158	150	138	108	
30	32	120/76	71	275	3.9	116	144	126	137	129	
31	50	138/90	70	269	3.8	134	171	173	138	110	
32	42	140/90	66	214	3.2	130	170	196	140	84	*
150+											
33	50	130/80	70	264	3.7	116	180	240	213	175	*
34	25	126/90	75	330	4.4	126	246	290	180	122	*
35	44	110/70	70	244	3.4	87	134	187	197	128	*
36	36	120/80	66	224	3.4	103	152	177	152	100	
37	41	130/90	66	215	3.1	131	215	262	230	104	
38	43	130/80	70	214	3.0	158	206	252	170	100	*
39	60	140/80	66	238	3.6	140	200	244	230	122	*
40	60	130/80	70	282	4.0	119	200	206	165	100	
41	34	130/80	68	248	3.6	153	209	236	214	148	*
42	64	110/70	63	225	3.6	168	—	—	—	—	

*=Glycosuria during test

common among the obese than in the general population.

It is, therefore, fair to assume that obesity tends to slow down the activity of an individual. Likewise, hypertension *per se,* especially when the heart, kidney or brain are affected interferes with the ability of the individual to engage in physical effort. When hypertension and obesity are associated in the same person, the organism tends to be greatly overburdened by the disabilities inherent in the two disorders, which compels him to curtail his activities sharply. Since it is a commonly accepted fact that exercise improves the tolerance for glucose, the enforced inactivity to which the patients studied have been subjected by the combined effects of obesity with hypertension very likely had at least some influence on the diminution of their glucose tolerance.

Finally, between the ponderal indices of 2.7 and 3.8, or up to 75 per cent overweight, no definite correlation was found between the degree of obesity and the abnormality of the glucose tolerance. Beyond the ponderal index 3.8 and 75 per cent overweight, there was a sharp rise in the incidence of diminished glucose toler-

TABLE 2 C.

Hypertension without obesity

Second-Hour Blood Sugar mg. per 100cc. Case No.	Age	Blood Pressure	Height Inches	Weight Lbs.	Ponderal Index (WT/HT)	Glucose Tolerance					
						F	½	1	2	3	
Below 135											
1	46	170/110	67	150	2.2	105	122	140	94	112	
2	54	190/110	68	150	2.2	118	170	160	118	130	
3	61	190/110	67	112	1.7	126	180	153	130	73	
4	46	198/100	66	142	2.1	122	178	170	112	61	*
5	41	180/130	63	152	2.4	78	112	112	70	73	
6	31	200/140	69	175	2.5	97	149	126	97	65	
7	35	160/110	67	147	2.1	141	131	135	110	100	
8	43	170/110	66	150	2.2	116	180	165	123	103	
9	47	160/110	72	170	2.3	100	137	133	126	84	
10	31	140/110	68	170	2.5	97	116	149	120	116	
11	56	170/106	67	136	2.0	97	148	166	97	100	
12	52	200/140	69	149	2.1	97	181	209	97	104	
13	51	170/120	64	140	2.1	104	214	153	115	97	
14	22	230/160	66	115	1.7	99	111	117	99	80	
15	25	170/110	65½	145	2.2	109	166	166	119	84	
16	46	200/120	67	137	2.0	126	170	152	103	97	
17	55	190/100	69	158	2.2	106	156	136	103	112	
18	43	190/130	69	168	2.4	118	156	180	94	92	
19	38	200/120	68	150	2.2	119	157	161	133	113	
20	40	160/120	69	176	2.5	97	152	152	109	97	
21	27	160/100	66	153	2.3	110	140	157	100	63	
22	43	170/120	66	148	2.2	109	140	109	112	91	
23	45	130/100	70	180	2.5	116	172	134	104	90	
24	42	150/100	71	180	2.5	98	172	138	121	90	
25	63	200/130	63	150	2.3	121	163	177	101	77	
26	41	180/120	68	128	1.8	104	127	154	134	142	
27	49	220/150	66	132	2.0	125	170	165	125	82	
28	59	200/110	65	130	2.0	90	126	134	113	75	
29	27	160/110	64	125	1.9	94	138	110	120	113	*
30	39	150/100	66	149	2.2	126	153	148	134	90	
31	37	170/120	68	143	2.1	97	112	115	126	112	
32	27	140/100	69	167	2.4	99	198	104	91	91	
33	41	170/100	64	143	2.2	106	144	153	122	86	
135 +											
34	36	200/140	66	155	2.3	118	144	166	136	84	*
35	60	160/110	66	146	2.1	133	—	140	148	136	
36	30	150/100	66	150	2.1	106	153	157	145	97	
37	37	170/116	64	145	2.2	123	149	161	145	94	
38	65	200/120	63	153	2.4	126	170	282	141	133	
39	39	230/160	67	157	2.3	101	138	158	142	107	
40	43	180/120	63½	153	2.4	103	138	142	138	94	
41	38	150/110	70	160	2.2	109	132	144	136	81	
150 +											
42	63	200/120	66	141	2.1	115	157	197	157	115	
43	44	200/130	65	163	2.5	105	179	200	182	72	*
44	41	200/130	68	167	2.4	129	211	230	166	106	*
45	69	180/110	69	164	2.3	129	185	256	240	113	
46	59	170/110	66	135	2.0	116	234	248	180	76	*
47	58	200/130	65	148	2.2	133	175	202	157	123	
48	54	170/110	66	140	2.1	100	166	202	186	86	*
49	46	160/100	66	159	2.3	144	209	255	197	136	*
50	57	190/120	68	171	2.5	126	223	215	210	103	*
51	42	170/120	70	155	2.2	119	192	215	170	110	
52	47	210/120	66	140	2.1	140	217	231	189	152	*

*=Glycosuria during test

ance tests, especially in the hypertensive obese group.

SUMMARY

1. A conventional oral glucose tolerance test using 100 grams of glucose was performed on 60 male adults with hypertension and obesity, 42 male adults with obesity without hypertension and 52 male adults with hypertension without obesity. The age distribution of the three groups was comparable. The ponderal index (weight in pounds divided by height in inches) in the

TABLE 3
Glucose tolerance in relation to diastolic blood pressure.

	Diastolic Pressure	Total Cases	Total Abnormal	Second-Hour Blood Sugar		
				150 +	135 +	Below 135
Hypertension and Obesity	140	3	2	2		1
	130	8	4	4		4
	120	13	10	9	1	3
	110	14	9	9		5
	100	18	15	12	3	3
	90	4	3	2	1	1
Total		60	43	38	5	17
Hypertension without Obesity	160	2	1		1	1
	150	1				1
	140	3	1		1	2
	130	6	3	3		3
	120	13	6	4	2	7
	110	16	6	3	3	10
	100	10	2	1	1	8
	90	1				1
Total		52	19	11	8	33

TABLE 4
Glucose tolerance in relation to systolic blood pressure.

	Systolic Pressure	Total Cases	Total Abnormal	Second-Hour Blood Sugar		
				150 +	135 +	Below 135
Hypertension and Obesity	250					
	240					
	230					
	220	2	2	2		
	210	3	2	2		1
	200	6	4	4		2
	190	7	5	5		2
	180	8	6	5	1	2
	170	13	6	6		7
	160	9	7	7		2
	150	8	8	4	4	
	140	4	3	3		1
Total		60	43	38	5	17
Hypertension without Obesity	250	1				1
	240					
	230	2	1		1	1
	220					
	210	1	1	1		
	200	12	6	4	2	6
	190	6	1	1		5
	180	4	2	1	1	2
	170	12	4	3	1	8
	160	7	2	1	1	5
	150	4	2		2	2
	140	3				3
Total		52	19	11	8	33

obese groups was above 2.7, and in the non-obese group was below 2.5. All blood pressure readings in the hypertensive groups were above 150/90. All known cases of diabetes mellitus, hyperthyroidism, cirrhosis of the liver, hepatitis or frank Cushing syndrome were excluded.

2. A second-hour, blood sugar value below 135 mg. was arbitrarily considered normal, 135-149 mg., slightly abnormal, and 150 or higher, grossly abnormal. Among the 60 obese hypertensives, there were 38 grossly abnormal glucose tolerance tests, or 63.3 per cent and 5 slightly abnormal tests, or 8.4 per cent. Among the 42 obese normotensives, there were 10 grossly abnormal glucose tolerance tests, or 23.8 per cent and 9 slightly abnormal tests, or 21.4 per cent. In the 52 non-obese hypertensives, there were 11 grossly abnormal glucose tolerance tests, or 21.1 per cent and 8 slightly abnormal tests, or 15.4 per cent. It was noted that beyond a ponderal index of 3.8 there was an increased incidence of abnormal tests in both obese groups.

3. The frequency of decrease in the glucose tolerance in obesity without hypertension is comparable to that found in hypertension without obesity. Where obesity and hypertension co-exist, decreased glucose tolerance occurs more frequently.

4. Age did not have a definite correlation with the decrease in glucose tolerance in our series.

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DISCUSSION

ALEXANDER MARBLE, M.D. (*Boston*): The findings of Doctor Drazin at first sight seem startling but review of the literature shows them to be consistent with those of others who have studied this problem, particularly with reference to obesity. Since 1920 many workers have carried out sugar tolerance tests in groups of individuals with a wide variety of conditions. Abnormal results have been reported in such diverse states as nephritis, pregnancy, hyperthyroidism, fractures, diseases of the liver, hyperpituitarism, disorders of the adrenals, apoplexy, infections, cancer, ulcerative colitis, arthritis and the two conditions studied by Doctor Drazin, namely hypertension and obesity. Doctor Drazin would agree, I am sure, that although the collection of such data is tedious and time-consuming, its interpretation is even more difficult.

Doctor Drazin has wisely avoided the use of words "diabetes" and "diabetic." These patients were not healthy persons. They were either obese or hypertensive or both; Doctor Drazin has informed me that, although ambulatory, many of them complained of easy fatigability, dizziness, headache, substernal distress on effort, exertional and nocturnal dyspnoea and occasional swelling of the feet. Because of this, physical activity had been greatly curtailed. Consequently, they were not ideal subjects on which to carry out sugar tolerance tests with a view to the diagnosis of diabetes and this is well recognized by Doctor Drazin. Having said this, however, let me hasten to add my belief that the question of genuine diabetes, mild or potential, in the group cannot be dismissed lightly. This can be determined only by careful periodic study of the same persons as time goes on.

I wish to ask Doctor Drazin if the matter of doing intravenous glucose tolerance tests on at least a part of the same subjects has been considered. The results might well be the same but in this way the factor of intestinal absorption would be ruled out. Are any figures available for the behavior of the blood phosphorous during the glucose tolerance test? Has Doctor Drazin made an analysis of the other points in the glucose tolerance curves, namely the fasting and the peak values? If so, were the results consistent with those presented today in which only second-hour values were considered? Does Doctor Drazin have figures regarding diabetes heredity in this group of patients? Finally, are follow-up studies with repetition of the glucose tolerance tests planned? Such would be most instructive over months and years of time, particularly if loss of weight can be achieved.

MORRIS L. DRAZIN, M.D. (*New York*): Among the patients followed up some lost weight, glucose tolerance became normal, confirming Newburgh's observations.

In the 154 glucose tolerance tests reported here there were 19 fasting blood sugar tests above 135. If one were to rely on the fasting blood sugar test alone, one would miss many positive cases.

Concerning the height of the blood sugar curve, with few exceptions whenever the second-hour blood sugar was elevated, there was a high peak. However, when the peak was elevated, the second-hour blood sugar was not necessarily elevated. I believe this work confirms the opinion of Mosenthal and others, that the second-hour figure is the key figure in glucose tolerance tests.

On random tests, all these patients were aglycosuric. If a patient had glycosuria, he was excluded from this series. Therefore all patients presented in this study were free from sugar in the urine, and apparently nondiabetic. They did not have any associated disease which would give an abnormal glucose tolerance test.

In regard to diabetes heredity, thorough studies were not made. Determinations of blood phosphorus were not made.

Intravenous tolerance tests were not feasible under the circumstances of our study. Furthermore, I believe that the oral glucose tolerance test is valid.

The Effect of Insulin on the Glucagon Content of the Pancreas

Studies of the Hyperglycemic-Glycogenolytic Factor of the Pancreas (HGF) in Normal and Insulin-Resistant Mice

Walter B. MacGrath, Jr., M.S.,
and James G. Snedecor, Ph.D., Amherst, Massachusetts

The work of a number of authors[1–4] indicates that a factor elaborated by the pancreas may bring about hyperglycemia by facilitating the conversion of liver glycogen into blood glucose. The literature concerning this factor has been adequately reviewed by Zimmerman[5]. This "anti-insulin" action was first thought to be due to a contaminant which occurred in amorphous insulin preparations, but subsequent studies[6, 7] showed that the hyperglycemic-glycogenolytic factor (HGF) was present in crystalline insulin, and that either insulin or HGF could be inactivated selectively by appropriate methods[8–12]. The term glucagon, which was originally suggested by Murlin[12] to designate the hyperglycemic material from the pancreas, has come into common usage. It now seems quite certain that HGF is produced by the alpha cells of the pancreatic islets, although cytological evidence of secretory changes is lacking.

In the search for a physiological mechanism which could explain the surprising tolerance to insulin of mice of the KL strain[13], it occurred to us that the hyperglycemic-glycogenolytic factor (HGF) of the pancreas might be responsible.

If, in response to a large dose of insulin, the pancreas of the resistant mouse can elaborate larger quantities of HGF than can the pancreas of the non-resistant animal, the action of insulin might be sufficiently counteracted to allow survival. It was the purpose of the work reported here to determine whether or not the pancreas of the resistant animal produces more HGF in response to high insulin dosage than the pancreas of an animal of a non-resistant strain.

MATERIALS AND METHODS

The insulin-resistant animals used in these experiments were of the KL strain; our original stock was supplied through the kindness of Dr. Herman Chase. Not all of the animals of this strain are equally resistant. The highly-resistant animals were selected as follows: Animals 35 days of age were given a subcutaneous injection of 200 units of insulin (Lilly, 500 units per ml). The dose was given in a single injection in the morning. The animals were not fasted prior to injection; food was withheld for one hour following injection. Only animals which survived this test were used as resistant animals.

The non-resistant animals were of two kinds: C57 Black, and a strain of white mice used at the Lilly Research Laboratories for the assay of insulin. No differences were detected in the response of these two non-resistant types. All animals used in the tests to be described were 40-65 days old; they were fed Purina laboratory chow and water *ad libitum.*

The amount of HGF which could be extracted from the mouse pancreas was taken as the criterion of HGF production. The method employed in the preparation and assay of the extracts follows. Animals were killed by a blow on the head and the pancreas removed as quickly as possible and placed in the extraction fluid (75 per cent alcohol 0.18 N with hydrochloric acid); later the tissue was minced. In the groups receiving insulin, the

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A portion of this paper was submitted by Mr. MacGrath as a thesis for the M.S. degree, University of Massachusetts.

This investigation was aided and the insulin generously supplied by Eli Lilly and Company.

mice were injected, food was withheld, and the animals killed one to two hours following injection.

The method for extraction is essentially that of Best, Haist and Ridout[14] as modified by Sutherland and deDuve[3]. Each extract represented the pancreatic tissue from five mice which received identical treatment. Small Erlenmeyer flasks containing 3 ml of the acid alcohol were weighed; after the five glands were added, the flask was reweighed and the acid-alcohol increased to 5 volumes. After the acid alcohol extraction of the tissue was carried out overnight in the cold, the tissue was removed, re-extracted with 2.5 volumes of acid alcohol for one hour in the cold, and the extracts combined. The *p*H was adjusted to 7.5 with ammonium hydroxide and the resulting precipitate was eliminated following centrifugation. To the supernatant fluid was added 4.5 volumes of ether-alcohol (1.7 volumes of absolute alcohol and 2.8 volumes ethyl ether), and this mixture was allowed to stand overnight in the cold. The resulting precipitate contained the HGF and insulin; it was separated by centrifugation and dried *in vacuo*. Just prior to assay the material was taken up in a chloride-phosphate buffer (20 ml 0.9 per cent sodium chloride plus 2 ml. 0.1 M tribasic potassium phosphate plus 3 ml. 0.1 M dibasic potassium phosphate, *p*H 7.4), so that one ml. equaled one gram of fresh tissue. This did not result in a solution, but the suspension was made as homogenous as possible, and 0.1 ml. of this mixture, representing 100 mg. of pancreas, was then tested for HGF content by determining its effect upon the blood sugar level of an anesthetized cat.

Mature non-starved cats anesthetized with nembutal or amytal were used for assaying the samples. In the earlier experiments, the test samples were injected and the blood samples drawn by passing the needle through the skin into the sapheneous vein. Animals handled in this way could be used in later assays, but when this was done the cats were not used oftener than every other day and care was exercised to avoid giving extracts representing similar treatments to one cat. In later assays the saphenous and femoral veins were exposed by an incision; this allowed the venipuncture to be made much more easily. These latter animals were not used for a second assay.

Blood samples were taken at five-minute intervals for the first 15 to 25 minutes following injection of the extract. The maximum hyperglycemic response was taken as the indication of HGF activity. This maximum usually occurred at five minutes, less often at ten, and only once as late as 15 minutes after the injection of the sample. Blood sugar determinations were determined by two different methods. In most of the assays, the Nelson micro-method[15] was used, and in some experiments a modification of the Somogyi method was employed.

RESULTS

The increases in blood sugar of the cats used in the assays are shown in Figure 1. (It is assumed that the rise in blood sugar indicates the HGF *content* of the pancreas; it would perhaps be more accurate to state that it corresponds to the *extractable* HGF.) Within each group the values are arranged in order of magnitude. The results are expressed in terms of the actual rise (in mg per 100 cc) in the blood sugar of the test animal. The rise in blood sugar expressed as a percentage of the control sugar value was not used because the hyperglycemic response seems to be independent of the pre-existing sugar level (at least, when in the normal range). Moreover, it is thought, for example, that an increase in blood sugar from 70 to 100 mg per 100 cc is no more significant that a rise from 90 to 120 mg per

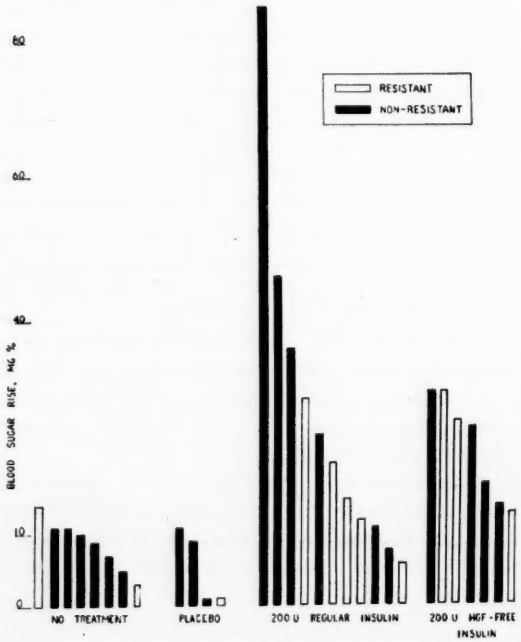

FIGURE 1. Increase in cat blood sugar in response to extracts of pancreatic tissue of insulin-resistant and non-resistant mice. Each value represents a single assay; each extract was assayed only once. Pancreatic tissue from five identically treated mice was combined in the preparation of each extract.

100 cc, yet when the rise is expressed as a percentage of the initial value, the former value would be considerably higher.

The most striking result apparent from the assay data is the considerable difference in the HGF content of the pancreas from insulin-treated and non-insulin-treated animals. When the assay values for all groups receiving insulin are compared statistically with the values for the groups not receiving insulin (Table 1, 1), a highly significant difference appears. Moreover, both the resistant and non-resistant animals respond to insulin by increased HGF production, and, as shown in Table 1, 6, the two strains do not differ in the degree of the response. Thus, although the amount of HGF produced by the pancreas is increased following high insulin dosage, such a mechanism cannot account for the difference in insulin tolerance in the resistant and non-resistant strains.

When the data for the two categories, untreated controls and animals given 200 units of regular insulin, are compared statistically a significant value appears (Table 1, 3). The one extreme value in the insulin-treated group (see Figure 1) cannot be satisfactorily explained but illustrates that most of the values are by no means maximal. In several of the assays, the test sample was followed (after 25 minutes) by administration of a standard U-40 insulin preparation (Lilly-ML 491,516) and when given in an amount equivalent to 0.05 ml per kg. produced a nearly maximal response; in every case this response was greater than the response to the test sample.

Control injections of distilled water were made in three groups of non-resistant and one group of resistant animals (indicated "placebo" in Figure 1) and the assay values were not significantly different from the results in the group given no treatment (Table 1, 7), indicating that the injection of the animals was, in itself, no stimulus to HGF production. When the data for "placebo" groups given control injections were added to the data for groups given no treatment to form a category of animals given no insulin and then compared statistically with the data for animals given 200 units of regular insulin (Table 1, 2), a t value indicating significance at about the .03 level was obtained.

The possibility existed that the HGF present in the injected insulin might be responsible for a part of the HGF appearing in the extracts. Therefore, a number of assays were made with extracts derived from animals injected with 200 units of an insulin preparation substantially free of HGF (Lilly, T-2536). It was found that extracts from animals receiving regular insulin did not differ in HGF content from those receiving HGF-free insulin (Table 1, 4). This indicated that the extracted HGF had an endogenous source. Extracts from both resistant and non-resistant animals injected with HGF-free insulin were tested, and again there was no difference in the response of the two groups as is well shown in Figure 1. When the data for all assays representing HGF-free insulin are compared with the data for either "no treatment" (Table 1, 5) or "no insulin" groups, a highly significant difference appears.

TABLE 1

Summary of statistical comparisons utilizing the t test†

Groups Compared	t value at .05 level	t value at .01 level	t value obtained
1. All mice given insulin: all given no insulin		2.92	3.92**
2. Mice given regular insulin: all given no insulin	2.23	3.17	2.62*
3. Mice given regular insulin: untreated controls	2.23	3.18	2.41*
4. Mice given regular insulin: mice given insulin free from HGF	1.59		0.54
5. Mice given insulin free from HGF: untreated controls		3.67	4.26**
6. Insulin-resistant mice given regular insulin: non-resistant mice given regular insulin	2.59		1.55
7. Placebo controls: untreated controls	2.23		1.50

†When the groups compared are of unequal size and their variances differ decidedly as was the case in most of the above comparisons, the usual t test is unreliable as it tends to give a larger number of significant values (for differences between means) than is warranted. In the majority of the comparisons in the table this was taken into consideration by calculating the variance of each mean separately according to a method suggested by Cochran and Cox[21].

**Highly significant *Significant

DISCUSSION

The lack of any difference between resistant and non-resistant animals in their pancreatic HGF content following the injection of 200 units of insulin indicates that the resistance to insulin of the KL strain cannot depend upon an increased capacity for HGF elaboration. The possibility exists, however, that the pancreas of the resistant animal releases more HGF into the circulation,

and that the amount of HGF remaining in the pancreas does not represent, in the two strains, the same ratio between the amount of HGF elaborated and the amount released. This possibility has not been tested.

The decided increase in HGF in all groups of animals given insulin was unexpected. This might be explained in two ways: In the first place, large amounts of exogenous insulin may provide a stimulus for HGF production, or, secondly, the great increase in circulating insulin may result in a retention by the pancreas of its HGF and insulin. A knowledge of the insulin content of the pancreatic extracts will be informative. If both insulin and HGF are decidedly increased in the extracts, the retention possibility would be supported, whereas if insulin is not increased in the pancreases of insulin-treated animals, then the stimulus must be specifically for HGF.

Although an increase in pancreatic HGF following large amounts of insulin cannot explain the insulin-tolerant character of the KL animals, the increase may contribute to the resistance by providing protection or "insulin antagonism" for a sufficient period of time to allow another defense mechanism to come into play. This possibility is suggested because the KL animals do not exhibit their characteristic resistance when the insulin dosage is relatively low, i.e., one to two units, and furthermore, because unpublished data indicate that animals dying from low dosages survive a shorter time than if the dosage is high.

As a working hypothesis, then, it is suggested that whereas low insulin dosages may not appreciably increase HGF and thus not give protection long enough for a more effective defense to be organized, high dosage results in increased HGF which provides transient protection for sufficient time for the secondary defense to come into play. It is this secondary defense which must be especially effective in the resistant animals. Experiments to test this hypothesis are under way.

Zimmerman and Donovan[16] found that their hyperglycemic preparations failed to protect mice against insulin-induced convulsions, and concluded that HGF could not be responsible for resistance to insulin, but in their work the hyperglycemic material was injected subcutaneously and it has not been shown that HGF can exert any affect when administered in this way.[17]

It is likely that the effects of HGF are transient following a single insulin injection because the material is broken down rapidly in the blood[2], but if the pancreas produces HGF continuously under the stimulus of high insulin dosage, hypoglycemia might be prevented until hepatic glycogen stores are exhausted. Almost normal blood sugars have been noted by us as long as one hour after large doses of insulin in mice, and others[9, 17, 18, 19] have shown that the continuous infusion of insulin (thus exogenous HGF) will result in prolonged hyperglycemia. Also, Pincus[4] showed in the dog that successive injections of small amounts of HGF could prevent the hypoglycemia which would ordinarily follow the administration of 2 units of insulin.

The role of HGF in the normal physiological scheme is not at all clear. Repeatedly, HGF has been spoken of as antagonistic to insulin in that it raises rather than lowers blood sugar. There is no indication, however, that HGF and insulin antagonize one another directly or even that they exert their effects at the same point in the metabolic system.

It may not be amiss to suggest that HGF functions in the physiological scheme by acting not as an antagonist to insulin but in a sense as a synergist. Sutherland and Cori[2] have shown that insulin free of HGF does not have a glycogenolytic action upon liver slices, whereas either HGF alone or HGF plus insulin does bring about the breakdown of glycogen in the slices. Although this has not been demonstrated *in vivo*, it is not unreasonable to think that HGF is necessary if insulin is to act effectively in increasing the availability of carbohydrate to extrahepatic tissues.

DEPLETION OF HEPATIC GLYCOGEN

The rapid depletion of hepatic glycogen after the administration of insulin may well be not the effect of insulin *per se*, but rather that of the HGF either accompanying the insulin when it is injected intravenously, or arising endogenously in response to the stimulus of exogenous insulin. This is substantiated by the fact that liver glycogen begins to fall immediately following insulin injection before the hypoglycemic effect of insulin becomes apparent[17].

Although the present study has not provided an explanation of the difference in insulin tolerance between the KL and other strains of mice, the demonstration of increased HGF in the pancreas following insulin is of importance, for it is the only instance that we are aware of which indicates a change in the HGF content of the pancreas as a result of experimental procedure. Recently, Bornstein[20] showed that the blood of alloxan-diabetic hypophysectomized adrenalectomized (ADHA) rats receiving growth hormone had a greater hyperglycemic effect than the blood of control ADHA rats when tested in ADHA animals. Whether or not this hyperglycemic effect is due to HGF has yet to be determined.

SUMMARY

Normal mice and insulin-tolerant individuals of the KL strain (reported by Chase, et al, in 1948) were compared as to their ability to elaborate the pancreatic hyperglycemic-glycogenolytic factor (HGF or glucagon). It seemed possible that a greater ability to produce the factor in response to massive doses of insulin might help explain the surprising insulin tolerance of KL animals. The KL animals used in the tests reported here had previously survived a single injection of 200 units of insulin.

Both normal and resistant animals were injected with 200 units of insulin. Animals receiving insulin were killed one to two hours following the injection and the pancreas extracted for HGF (and insulin) by a modification of the method of Sutherland and deDuve. Pancreatic extracts were similarly prepared from animals of each strain which received no insulin. Extracts were assayed for HGF activity, using cats. The maximum blood sugar rise in mg per 100 cc was taken as an indication of the HGF content. (It is assumed that the extractable HGF corresponds to the HGF content of the pancreas.)

The results indicated that (1) following insulin the pancreas of both strains contained decidedly greater amounts of HGF than normally and (2) there was no significant difference between the insulin resistant animals and the others in this respect. This means that the ability to elaborate HGF (as estimated by the amount extractable from the pancreas) either normally or as a consequence of insulin injection does not seem to be a point of difference between the resistant and normal animals, but does suggest a physiological role for the hyperglycemic-glycogenolytic factor.

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Diabetes in Industry

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The problem of diabetes in industry is of importance for two major reasons: 1. The improved care of the diabetic keeps him alive longer, and permits him to work and lead a productive life. 2. Industrial medicine plays an important role in public health. According to recent statistics of the Metropolitan Life Insurance Company, there are about 250,000 diabetics in the labor force in the United States, and the number is growing from year to year. Industrial medicine can render a service to both the patient and the physician in the diagnosis and supervision of diabetes, and an opportunity is afforded to gather valuable data concerning the disease.

This review has been prepared in an effort to ascertain the present status of the diabetic in industry and the methods by which industrial medicine participates in the practice of preventive medicine. The study was divided into two parts—first, a survey of the employment of diabetics in various unrelated industries; second, the study of a group of diabetics under our supervision in the Third Avenue Transit System of New York.

EMPLOYMENT OF DIABETICS BY 63 COMPANIES

Data were obtained by sending a questionnaire to the medical directors of 348 companies in the United States, its possessions and Canada. (A list of these directors was obtained from the files of the Industrial Medical Association.) All types of industry were represented. The questionnaire was limited in scope in order to insure maximal response. We received 70 replies, but 7 contained inadequate information. In view of the relatively low proportion of replies, it is uncertain that the results are representative. Yet an analysis of the 63 providing suitable data, does give some indication of current practices in a segment of industry.

The total number of employees represented was 780,823. The following industries were included in the survey: sugar cane plants, aircraft, oil, steel, chemical, telephone, textile, railroad, washing machine, rubber, optical, film, paper, radio and television manufacturing, automobile, tire, can manufacturing, utilities, whisky distillers, transportation, baking and soap.

The incidence of diabetes. In regard to 24 of the 63 companies, the number of diabetics employed was not known. Reports from 39 companies, with 286,622 employees, indicated a total of 1,485 diabetics—an incidence of 0.5 per cent.

Employment policy regarding diabetics. Forty-three of the 63 companies employed known diabetics, 20 did not. Thirty-three companies restricted the diabetic to non-hazardous work; 24 companies had no restriction and 6 companies had no set policy.

Attitude towards veteran employee developing diabetes. Thirty-eight companies permitted an employee who developed diabetes to continue his job, while 24 companies restricted the type of work after diabetes was discovered. One company reported no set policy.

Time lost from work. Sixty of the 63 companies had no available statistics relative to time lost by the diabetic and nondiabetic employees. Three companies reported "the same" time off for both categories.

Calibre of work. Two companies reported that the diabetic performed "better" than the nondiabetic. Forty-four reported the "same" calibre of work in both groups. These reports probably represent opinions rather than accurate evaluations. In 17 companies it was undetermined.

Care of the diabetic. In 4 companies the diabetic was under the care of the company doctor alone. In 36 companies, he was under the care of a private physician. In 22 companies he was under the care of both private and company physicians. One company had no report. Thirty-eight companies performed periodic urine tests; 23 did not and 2 did not report.

EMPLOYMENT OF DIABETICS IN THIRD AVENUE TRANSIT SYSTEM, NEW YORK

An analysis was made of all available information concerning the diabetics in the Third Avenue Transit System from 1947 to 1952. The company maintains a medical department approved by the American College of Surgeons. The major functions performed by this

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department are (1) pre-employment and periodic examinations; (2) care of illness (when the employee is not under the care of his own private physician) and accident cases; (3) consultation and laboratory services for use of the employees and their physicians. All pre-employment and periodic examinations include a routine urinalysis. When glycosuria is discovered, urine tests are repeated and blood sugar determinations are made. When necessary, a glucose tolerance test is performed.

Data regarding diabetic employees. Of the 3,508 employees (3,252, male and 256 female) there were 40 known diabetics, 39 males and 1 female, an incidence of 1.1 per cent. The age of the diabetics varied from 32 to 68 years and averaged 54.5 years. The age of all employees varied from 19 to 65 years and averaged 46.1 years. The age at onset of diabetes varied from 31 to 65 years and averaged 50.4 years. The average duration of employment prior to the discovery of diabetes was 16.8 years; the maximum was 39 years. Four persons had diabetes of several years duration prior to employment. The duration of employment since discovery of diabetes averaged 3.9 years, varying from 0.5 to 22 years.

Various occupations were represented among the diabetics: there were 17 bus operators, 10 mechanics, 4 office workers and 9 miscellaneous workers (stockmen, laborers, elevator operators, superintendents. Of the total number of 3,508 employees there were 1,873 operators, 953 mechanics, 336 clerical workers and 346 in miscellaneous jobs.

The diagnosis of diabetes was made by the company medical department in 18 cases, by a private physician in 17 instances, and by other or unknown sources in 5 cases.

Treatment. Eleven employees took insulin regularly, 16 took no insulin and 6 took insulin irregularly. In the remaining cases no data were available.

Applicants with diabetes requiring treatment with insulin were not rejected except for the position of bus operator. For such persons, we recommended employment in other work.

Diabetic control was classified in four categories: good, fair, poor and unknown. A person was considered under good control when he maintained his body weight, had minimal glycosuria, and absence of acetonuria. Fair control was signified by moderate to severe glycosuria, maintenance of body weight, and absence of acetonuria. Poor control was considered when the person lost weight, had severe glycosuria, and intermittent acetonuria.

Seven patients maintained good control, 6 fair and 3 poor. In 24, the status was undetermined. Seven of these 24 are no longer with the company. The remaining 17, or 43 per cent of the total number of diabetics, did not take advantage of the opportunity to cooperate with the medical department.

Ability to work. Twenty-seven employees were able to continue in their jobs. Five were permitted to continue as bus operators when they were not taking insulin. One patient who had pulmonary tuberculosis was unable to work because of his tuberculosis. Five patients were retired on reaching the prescribed age limit. Two resigned for reasons unrelated to diabetes. All of these patients were employed at the time of this study.

Absenteeism. A meticulous study was made of absenteeism in the Third Avenue Transit System for the 9-months period from February to October 1951. Absenteeism was divided into three categories: illness, accident and non-medical. Five of the 40 diabetics were not employed during this period of study, having been pensioned previously. The remaining 35 were compared to the total group and the results are shown in Table 1.

TABLE 1

Number of days absent per employee per year

	Sickness	Accident	Non-medical
Total group	11.81	0.69	7.10
Diabetics	26.2	0.80	4.60

The absence for sickness of the diabetic group requires a word of explanation. Two individuals were absent for long periods of time; one patient with pulmonary tuberculosis was absent the entire 9-months period of study because of tuberculosis and not his diabetes. The other was absent 146 of the 273 days because of an ulcer on the foot. These two patients represent only 6 per cent of the diabetes, but 61 per cent of the number of days absent with illness of the diabetic group.

The time off for illness for the other 33 diabetics (94 per cent of the cases) was 10.8 days per employee per year. This is approximately the same illness absentee rate as for the nondiabetic group (not excluding exceptional chronic cases).

CALIBRE OF WORK

An effort was made to compare the calibre of work, as measured by the accident rate, performed by the diabetic and nondiabetic bus operators.

Thirteen of the 17 diabetic bus operators drove in the New York City routes. The statistics for the diabetic as compared to the total group are shown in Table 2.

TABLE 2

Number of accidents per man in 2-year period from July 1, 1950 to June 30, 1952

	300 Nondiabetic Operators	Diabetic Operators	Number of cases
1 st 2 years of driving	5.8		0
3rd year of driving	5.2		0
4th year of driving	5.3	5.6	6
5th year of driving	2.7	3.6	5
6th year of driving	3.3		
7th year of driving	3.2	3.0	2
			13

Although from a statistical viewpoint, the number in the diabetic group is deemed insufficient to permit a conclusion, the data for the diabetic group seem not far removed from the others. Further, both seem to show a sharp decrease in accidents after the fourth year of operation.

DISCUSSION

Industrial medicine can render service to the diabetic in the following ways: (1) the early detection of diabetes through pre-employment and periodic medical examinations; (2) cooperation with the private physician in the care of the disease; (3) cooperation with the personnel department in the proper placement of the diabetic; (4) education of both management and labor in the problems of the diabetic with improvement of labor relations; and (5) collection of statistics for study of diabetes on a large scale.

EARLY DETECTION OF DIABETES

Wilkerson and Krall[2] found in 1947 that the incidence of diabetes in Oxford, a New England town, was 1.4 per cent of the population tested, including 0.6 per cent in which diabetes had not previously been recognized. In an industrial survey concluded in 1942, Gates[4] tested 109 selected individuals (believed most likely to have diabetes) among a total of 1800 employees, by means of glucose tolerance tests. There were found to be 20 diabetic persons among the 1800; in 12 of these cases the disease had not been previously diagnosed.

The incidence of unrecognized diabetes in industry depends on a number of factors, including the age distribution of the employee and the type of medical service obtained from the company medical department and independent of the company.

The relationship of sex distribution of the population to the incidence of diabetes is at present undetermined. Although the mortality statistics show a higher death rate from diabetes for females, the Oxford Study[2] reveals almost an equal incidence in the male and female population. Our company employs 3,252 males and 256 females, a ratio of 12.7 to 1. In the United States, the total labor force is 62,416,000[1]. Of this total there are 43,334,000 males and 19,082,000 females, a ratio of 2.2 to 1. Our company, therefore, has six times the ratio of male to female employees as the general labor force.

One would expect to find more unrecognized diabetes in a company employing older individuals and with inadequate industrial and private medical care.

The age distribution in our company is higher than that of the general population (Table 3). The average age in our company is 46.08 years. The incidence of diabetes should be greater than in the general population because of this high age composition. Our incidence of 1.14 per cent as compared with that of 1.7 per cent in the Oxford Study[2] is of even more significance in view of the difference in the age distribution of the two groups, and undoubtedly means that there are still many cases of undiagnosed diabetes in our company.

TABLE 3

Comparison of the age distribution of the employees of the Third Avenue Transit System with the population of Oxford, Mass, and with the population of the U. S.

	Percent in each age group.		
	Third Avenue Transit	Oxford, Mass.[2]	United States[3] (1945)
Under 15	0	24.8	25.2
15 to 24	0.3	16.1	17.0
25 to 34	13.4	16.5	16.1
35 to 44	29.0	13.7	14.0
45 to 54	38.0	11.0	11.8
55 to 64	19.3	8.3	8.7
65 to 74	0	6.4	5.0
75 and over	0	3.2	2.2

In our company, the employee is exposed to independent medical care, because he is required to present a doctor's certificate prior to his return to work following an absence of five days or more. In spite of this medical care, our company's medical department still discovered 45 per cent of the diabetics in our employ.

The incidence of diabetes in the survey of other industrial plants was only 0.5 per cent. We doubt that the incidence of diabetes is any greater in our company than in any other industry or in the population at large, but that constant vigilance has resulted in early detection and proper treatment of many undiagnosed diabetics.

Cooperation of employers with the local diabetes associations in conducting intensive case-finding cam-

paigns would be especially valuable in smaller plants, where there is no in-plant medical supervision. Since approximately 75 per cent of the smaller industrial organizations employ part-time physicians for emergency care and first aid[5] the program could be carried out with the help of these physicians. Routine examinations for all employees seen by these physicians would increase the early detection of diabetes.

COOPERATION WITH PRIVATE PHYSICIANS

The majority of the diabetic employees remain under the care of their private physicians. Dublin and Marks[6] report success with an informal type of program in which the company offers its facilities which the employee may use according to his desires. The services of the staff physician and the medical laboratory are available to those who wish to use them, but there is no forced supervision. Diabetic employees may have their own doctors take complete responsibility for their treatment if they so desire. In the judgment of company physicians they receive reasonably good cooperation from diabetic employees.

Because of the responsibility to public safety, the medical department of a transit system cannot maintain this informal type of medical supervision; a comprehensive program must be established. It was our hope to establish a rapport with the patient and his private physician by offering the facilities of our laboratory, nutritional service and internists. The desired close relationship was difficult to obtain because the diabetic operator feared the loss of his job if we discovered that he needed insulin. A few of the operators who were taking insulin attempted to hide this fact. As a result, it has become necessary to employ the aid of both labor and management in insuring the proper follow-up.

Diabetics are required to have routine examinations at regular intervals in the company medical department. The care of the patient remains in the hands of the private physician. Reports of our findings and recommendations are submitted to him. If an operator who has been taking insulin can control his diabetes on diet alone, he is permitted to return to bus operation. Those who require insulin regularly are transferred to other positions.

The importance of close cooperation between the private and industrial physician cannot be over emphasized. Together, they can alleviate the fears of the diabetic concerning his employment, while insuring him of proper care. Additional facilities are made available to the private physician, while the industrial physician benefits by being able to maintain a close follow-up of the employees.

PROPER PLACEMENT OF DIABETIC

The proper placement of the diabetic in industry depends upon cooperation between the industrial physician and the personnel department.

The majority of large industrial organizations will employ a diabetic but place him in a non-hazardous job. When a veteran employee develops diabetes, he retains his job unless it is hazardous to himself or the public. Studies show that the work record of diabetics in industry is generally satisfactory as compared with nondiabetics. In our experience, with the exception of two individuals who had unusual complications, our diabetic employees had the same absentee record as nondiabetics. Dublin and Marks[6], in a study of 92 known cases of diabetes, showed excellent absence records in 40 per cent, average in 19 per cent and unsatisfactory in only 15 per cent.

Most diabetic workers are over the age of 40 and are valuable employees because of their long service and experience. Retaining them in jobs for which they are trained and in which they are experienced is good management.

Workers who become diabetic seldom need to change their jobs, although in exceptional cases a shift may be desirable because of a change in the diabetic's physical condition. Hurwitz[7] feels that the degenerative complications of the disease, especially peripheral vascular disease, make the diabetic unusually susceptible to trauma. It is interesting to note that our absentee records show that the time off for industrial accidents was no greater in the diabetic than in the nondiabetic.

A guiding principle in the placement of a diabetic is that he should not be in a position where, as a result of insulin reaction, he would endanger the lives of others as well as his own[6, 8]. Fowler[9] recommended that diabetics not be permitted to drive planes, locomotives or buses, or work at heights. However, we permit diabetics who do not require insulin to drive, since we feel that they are not a public hazard. Except where the factor of public and individual safety is concerned and the potential danger of an insulin reaction exists, we feel that a diabetic is capable of doing any job a nondiabetic can do.

EDUCATION

Education of Management. Management must be educated to have a favorable attitude toward the diabetic. Fair treatment of employees with diabetes leads to better

industrial relations. An unfavorable attitude is detrimental in that it leads to attempts at concealment of the disease, discouragement and discontent amongst diabetics; and a higher rate of unemployment.

One of the reasons put forth for the refusal to hire a diabetic is the increased cost of insurance and pension programs. This is refuted by a personal communication from Dr. Harry E. Ungerleider, Director of Medical Research of the Equitable Life Assurance Society, of the United States.

"The companies have not felt it necessary to add one penny to the premium because of the presence of diabetics in the group, and from a sickness and health insurance standpoint, that is, insurance payable either in weekly benefits, hospitalization or medical care, the diabetics have been no problem to us at all. We do employ diabetics as members of our organization and the only restriction we place upon them, of course, is that they must be under the care of a physician. From an ordinary life insurance standpoint, we insure diabetics who are controlled by diet or by insulin. As a matter of fact, we have been taking diabetics for the past twenty-five years if one would look at our formula. All in all, I do not think that diabetes is an insurance problem."

Education of labor. "The American Federation of Labor has a deep interest in the handicapped workers and their employment opportunities and this of course applies to the diabetic." This statement[10] is credited to Mr. Louis Hines, Secretary to the late Mr. William Green, The American Federation of Physically Handicapped, a subdivision of the American Federation of Labor, which is striving towards legislation in behalf of diabetic workers and realizes that some consideration must be given these people in order that their skills should not be lost or they be deprived of earning a livelihood.

Cooperation of labor is essential. They can be of great value in negotiating with diabetic employees in making special provision for transfer from hazardous to non-hazardous jobs. It is a responsibility of labor as well as management to see that a diabetic employee receives proper medical care, thus insuring him of earning his livelihood.

Education of the diabetic employee. The diabetic employee must be taught that his disease, properly cared for, does not pose a problem in industry. He must be taught the necessity of maintaining good medical care, and the importance of close cooperation between his private physician and his company medical department. He must be educated to treat his disease without embarrassment. His fellow employees should be notified of his disease so that emergency care may be rendered if necessary.

In our company the medical department impresses the diabetic employee with the fact that his record, good or bad, influences the attitude of the company towards all diabetic employees. We also emphasize that there is no need for concealment of the disease, since diabetics are not penalized by loss of their jobs. They may be transferred to other occupations for their own good as well as for public safety.

COLLECTION OF DATA

Industrial medicine can collect vital statistics concerning diabetes. Statistics as to the incidence of the disease, relative time off from work due to illness, and proneness to accidents, can only be obtained if large industrial organizations keep accurate records. Studies as to relative control of the disease and the development of degenerative complications, could be made by alert medical departments having the opportunity of following employees for long periods of time, and by collaboration between the private and industrial physician. A planned program utilizing the available facilities is necessary.

SUMMARY

Data concerning the diabetic in industry have been collected by means of a questionnaire, from 63 companies, representing 780,823 employees. The known incidence of diabetes among 286,662 employees of 39 companies reporting it was 0.5 per cent. Forty-three of the 63 companies employed known diabetics; 20 did not. Thirty-three companies restricted the diabetics to non-hazardous work. Twenty-four companies had no restrictions and 6 had no set policy. Thirty-eight companies permitted an employee who developed diabetes to continue in his job; 24 companies restricted the type of work after diabetes was discovered and one company reported no set policy.

A special study was made of diabetes among 3,252 male and 256 female employees of the Third Avenue Transit System in New York. There were 40 diabetics—39 males and 1 female, representing an incidence of diabetes of 1.1 per cent. The diagnosis was made by the Company Medical Department in 18 cases (45 per cent), by private physicians in 17 cases and by an unknown source in 5 cases. The age of the diabetic employee of this company varied from 32 to 68 years, an average of 54.4 years. The age of all employees varied from 19 to 65, with an average age of 46.1.

Two diabetic employees were absent from work for

many months, one because of tuberculosis, the other because of an ulcer on his foot. The remainder of the diabetics had an illness absentee rate of 10.8 days per year, which is approximately the same as for the nondiabetics. The accident absentee rate was the same in the diabetic and nondiabetic groups. The non-medical absentee record was lower in the diabetic than in the nondiabetic group—4.6 days absent per employee per year as compared to 7.1 for the nondiabetic group. The calibre of the work as measured by accident rate in diabetic and nondiabetic bus operators was the same.

Industrial medicine can offer a great service to diabetes in the early detection, supervision, proper job placement and education of the diabetic in industry. It can play an important role in the furtherance of our knowledge of the disease by the careful collection of data concerning diabetics in industry. Cooperation between the industrial physician and the private physician is essential. Greater vigilance of plant and independent medical care will result in the early detection of many undiagnosed diabetics.

ACKNOWLEDGEMENT

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Objectives of the Clinical Center of the National Institutes of Health

The United States now has a medical research establishment as fine as any in the world. This building, in its unique and original design, supplies the facilities that are essential for the close interworking of clinical and laboratory research scientists which is required by the intricacies of the search for the cause and treatment of diseases such as heart disease, mental illness, cancer and the other killing, crippling, and chronic diseases with which we will be working. The Clinical Center will make possible research of a very high caliber: our real job now begins.

Medical research is an intellectual pursuit. Its success depends entirely on the capability of the individual. If we are to succeed in this great undertaking, we must continue to attract staff of the highest professional qualifications and continue to maintain an environment in which scientific excellence is the major value. We want to create in this building the atmosphere of excitement, of high expectation and a knowledge of the happiness that can be achieved in serving mankind—the things that are common to all great research institutions.

We want our patients to feel they are our colleagues in research and to experience this same atmosphere. They will receive the best care that medical science can provide. Our moral obligation to do our best to treat the sick is paramount. Clinical studies will go forward within limits set by the welfare of patients. Not only is this a moral imperative—but it is the only way that sound clinical research can be done. These objectives and principles will guide the National Institutes of Health.

From extracts from remarks of the director, National Institutes of Health, at the dedication of the Clinical Center, by William H. Sebrell, Jr., M.D., in Public Health Reports, September 1953

The Obese Diabetic

G. O. Richardson, M.D., Newcastle upon Tyne, England

The association between diminishing carbohydrate tolerance and obesity is well known[1,2,3]. Newburgh and Conn[4,5] showed that carbohydrate tolerance was restored to normal by adequate weight reduction in a group of obese diabetics. They considered that, in this type of diabetes, obesity was the principal abnormality and hyperglycemia was a secondary phenomenon, and that these patients were fundamentally different from other diabetics.

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OBSERVATIONS OF SUGAR TOLERANCE

I have studied the effects of treatment in 34 cases of diabetes with obesity (illustrated in Table 1). Glucose tolerance tests with blood sugar determinations by the Folin-Wu method were done before treatment and were repeated after adequate weight reduction had been achieved. The patient had been on a diet containing 300 gm. of carbohydrate for three days before each test.

Although in every case the fasting blood sugar was lower after treatment, in only 10 was it less than 120 mg. per 100 cc. In 24 the whole curve remained charac-

TABLE 1
Results of glucose tolerance tests

		Before treatment Blood sugar in mg. per 100 cc.					After treatment Blood sugar in mg. per 100 cc.				
Case No.	Age	Fasting	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fasting	½ hr.	1 hr.	1½ hrs.	2 hrs.
457	63	240	320	390	380	350	200	255	310	290	234
425	55	200	290	340	220	145	130	146	190	300	210
356	56	340	360	460	430	420	150	210	225	300	220
319	64	215	280	380	360	290	185	270	350	290	300
506	63	190	290	370	320	260	140	250	300	310	190
264	49	235	390	470	290	270	155	220	180	175	125
329	61	310	390	460	380	410	165	210	300	310	250
324	59	330	440	480	540	440	140	200	300	350	260
124	50	160					120	205	290	270	175
191	53	230	320	290	260	240	155	260	290	245	240
381	50	175	300	400	300	230	170	220	250	230	210
197	56	220					150	240	330	270	175
132	62	330					190	400	380	250	305
819	53	255	300	370	230	230	190	210	310	310	300
357	50	280	380	370	320	310	240	300	390	370	300
530	62	235	340	410	290	250	175	225	250	250	185
212	50	185	340	290	340	260	170	150	220	220	185
316	62	300	430	510	540	500	145	190	300	235	225
210	63	280					250	340	370	310	280
209	48	280	350	410	450	330	205	220	250	230	205
226	55	180	260	290	300	260	170	185	380	310	190
320	67	240	270	400	400	340	170	235	360	340	240
462	60	230	290	340	380	210	155	250	290	245	210
517	63	340	390	460	600	500	170	250	240	195	200
439	63	390	310	410	360	350	115	155	185	185	240
551	54	165	280	340	260	250	110	290	210	235	200
255	51	260	340	390	340	250	115	250	300	200	165
297	66	280					100	290	330	300	160
806	35	185		326		200	100		210		185
426	63	125	210	265	210	135	102	205	200	200	105
446	43	155					100	170	210	135	110
164	50	170	200	240	200	200	90	195	280	145	75
422	61	330	410	430	380	330	95	140	180	140	115
354	57	175	220	205	170	160	115	175	180	95	90

teristically diabetic and of the remaining 10, 5 showed abnormally high levels after taking glucose, with persistent elevation at the end of two hours. In 3 others the blood sugar reached a level of 200 or more during the test, although the fasting and two-hour levels were within normal limits. In 2 cases the results approximated the upper limits of normal variation for this test.

DISCUSSION

Although at variance with the findings of Newburgh and Conn[4, 5] the persistence of abnormal glucose tolerance tests after adequate weight reduction and disappearance of all diabetic symptoms is in keeping with the fact that many people in apparently normal health are discovered to have diabetes. Routine medical examinations for life insurance and for military service have disclosed people in this group[6]. Wilkerson[7] studied the blood sugar of approximately 70 per cent of the total population of Oxford, Mass., and found a large number of people with abnormally high levels without symptoms of diabetes. Experimentally, it has not been possible to produce diabetes by over-feeding alone, but Allen[8] has shown that it can be produced by fattening partially depancreatised dogs. By analogy, it would seem that this experimental form of diabetes is similar to the diabetes of the obese person who becomes free from symptoms while retaining hyperglycemia after weight reduction.

If the mild diabetes associated with obesity and the diabetes requiring insulin treatment were etiologically distinct conditions, then one would expect considerable differences in the clinical manifestations. Polyneuritis, retinitis and cataracts are conditions which are closely associated with diabetes. In Table 2 it is shown that there is a similar incidence of these in the two types of diabetes studied.

The duration of diabetes in the two groups was similar, although there were more cases of long-standing diabetes among those who required insulin. (Table 3)

Acidosis is uncommon in obese diabetics, but does occur in association with infections and then insulin has been required to assist prompt recovery. Ketosis with coma has not occurred in obese diabetics in my experience.

It has been claimed that diabetes is inherited as a Mendelian recessive characteristic; there is at least no doubt that there is a greater incidence of diabetes in the relatives of diabetics than in those of a control population. The incidence of diabetes in parents and siblings is similar in cases of diabetes with obesity and in cases of diabetes requiring insulin treatment. (Table 4) Moreover, in the same family both diabetes requiring insulin and mild diabetes with obesity occur.

OVERWEIGHT BABIES

Children with a birth weight of over 8½ lbs. occur in from 5 to 7 per cent of all full term pregnancies. The birth of an unduly high proportion of heavy babies is a characteristic feature of the history of women who have diabetes at the time of conception, as well as of those who subsequently develop it. Of the 107 obese female diabetics considered in this paper, 76 have borne children and of these, 41 gave a history of having at least one child in excess of 10 lbs.

Thus, in the occurrence of complications, with the exception of diabetic coma, in heredity and in the frequent birth of unduly large babies, the obese diabetic is comparable to other diabetics. These points of similarity suggest that the attempt to separate the two groups into specific etiological entities is fallacious.

TABLE 2
Complications of diabetes

Type of diabetes	No. of Patients	Polyneuritis		Retinitis		Cataract	
		No.	Per cent	No.	Per cent	No.	Per cent
Diabetes treated with insulin:	277	72	26	21	8	26	9.5
Mild diabetes with obesity:	107	21	19.6	8	7.5	6	5.6

TABLE 3
Duration of diabetes

Years of diabetes	Diabetes treated with insulin per cent	Mild diabetes with obesity per cent
0-5	64	75
6-10	20	15
11-15	13	8
16-20	2	2
over 20	1	0

TABLE 4
Heredity

Type of diabetes		Diabetes in parent or sibling
Diabetes requiring insulin treatment	277	32
Mild diabetes with obesity	107	24

SUMMARY

1. After weight reduction, the glucose tolerance tests in the majority of a group of obese diabetics remained abnormal.

2. It is suggested that prolonged obesity leads to diabetes in a group of people who previously had latent diabetes.

3. The clinical similarity between mild diabetes of middle-aged obese patients and diabetes requiring insulin treatment has been emphasized and suggests that subdivision into specific etiological groups is misleading.

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The Relation of Water Balance to Weight Control

Despite the intricacies and interrelationships of the chemical mechanisms in the anabolism and catabolism of carbohydrates, fats and proteins, one still cannot circumvent the laws of energy conservation; and a person who gets fat must take in more than he expends. Contrariwise in the process of weight reduction, the accounts must show a negative balance—a greater expenditure than intake of energy . . . The scales often play us false and disclose water losses from the intra- and extracellular body compartments—a fact which accounts for the continued preying upon the public by multitudes of fake obesity cures involving sweating and diuretic agents; but the regimens of this type which show any lasting results are always accompanied by dietary restriction (of energy intake) . . . Most persons will, of course, lose water, rather rapidly at first, due largely to the fact that endogenous protein catabolism has been increased (to supply the energy deficit some protoplasm is consumed as well as stored fat) and there is coincident urinary loss of intracellular electrolyte and water. The scales will show in the first week a five or even 10 pound weight loss—to the elation of the unwary dieter. Subsequent weeks will show much lesser losses of poundage and some no loss at all, or even small gains.

There are some individuals who will lose no weight whatever, even on the most perfectly organized reduction dietaries, for two weeks or more. There will then follow a sharp weight loss; and at the end of a month or two, both types of individuals—i.e., the early fast losers and the slow losers—will be found to have adjusted their water equilibria to the new metabolic situations and both will have yielded about the same poundage . . . The desired end in the treatment of obesity is to lose the excess fat. To accomplish this, the fat must be metabolically burned. Since fat is a high calorie foodstuff and yields approximately 9 calories per gm.; and since from a practical point of view one can, in reducing regimens, only allow a deficit of about 1000 calories to be made up by body fat and since fat depots hold very little water (in contrast to protein and carbohydrate depots)—it may be seen that only about 100 gm. of fat can be burned off each day. Thus if we "reduce" in ideal fashion, that is, lose nothing but fat in the process and conserve all our substance (muscle, visceral protein, etc.), we should lose only 700 gm. per week or about 1¼ pounds.

We cannot so regulate a diet, however, that in weight reduction of any magnitude some protoplasm (presumably useful) will not be coincidently lost; but in planning a campaign to lose weight, it will be well to keep in mind that an average over the months of 2 pounds per week is all that can be achieved without loss of tissues that one doesn't care to lose . . . but little fat can be burned per day in terms of poundage, and that the frequently practiced daily examination of the scales reflects only water balance, leading to short-lived euphoria in some and depression in others. It is a wise rule to insist on weighing at intervals of two weeks to one month, for thus the inequities of water metabolism will be smoothed out.

From *Obesity*, by John Eager Howard, M.D., in the Maryland State Medical Journal, March 1953

Transient Diabetes with Coma Following Short Term Excessive Consumption of Carbohydrate:

A Case Report

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The onset of diabetes after acute dietary excess in man is considered doubtful, and a review of the literature reveals that no such cases have been reported. It is the purpose of this paper to present the case of a patient who manifested the entire clinical and functional picture of diabetic coma following the repeated ingestion of large amounts of carbohydrate, over a short period of time, and who completely recovered after adequate treatment.

METHODS

Routine fasting blood sugar determinations were done on venous blood according to the method of Folin and Wu; the normal values in this laboratory range between 90 and 110 mg. per 100 ml. Glucose tolerance tests were done by administering orally 0.75 gm. of glucose per kg. of body weight, dissolved in 250 cc. of water. Blood sugar determinations in these instances were done according to the method of Hagedorn and Jensen on capillary blood taken before and at 30, 60, 90, 120 and 180 minutes after ingestion of glucose. Quantitative and qualitative tests for sugar in the urine were made by the Benedict Method, using samples taken at the same time.

CASE REPORT

A 62-year-old man was admitted to the medical ward of the University Hospital in Rome on December 31, 1950, in a comatose state. He had had nauseau, vomiting, abdominal pain, and progressive stupor of two days' duration. The patient had enjoyed good health until 1946 when he developed acute ulcerative colitis. Medical treatment was unsuccessful and a colostomy was performed with complete relief of symptoms. The patient was discharged from the hospital after an uneventful postoperative course of 40 days, and the colostomy orifice was closed after six months.

There was no family history of diabetes, and the past history was otherwise noncontributory.

On December 22, 1950, the patient developed pneumonia. The diagnosis was made on a clinical basis; x-ray was not available. Penicillin was given and there was disappearance of all clinical symptoms at the end of three days. On December 27, 1950, because of a penicillin reaction, the drug was discontinued.

The patient was emaciated; there were moderate dehydration and weakness and his doctor advised him to take fresh fruits and sweetened fluids. This prescription the patient's wife applied so conscientiously that, according to her, in a period of two days she managed to have her husband eat approximately 4.4 lb. of cane sugar and 6.6 lbs. of honey.

On the afternoon of December 30, the patient began to experience abdominal pain, nausea and vomiting; he became progressively stuporous. Polyuria was noted and the urine was found to contain 6.2 per cent sugar. Physical examination on admission revealed an acutely ill patient in a state of coma. Respirations were rapid and shallow and there was a strong acetone odor on the breath. The skin, tongue, gums and lips were dry. A rash, which was attributed to a penicillin reaction, was present. There was muscular hypotonia. The eyeballs were soft and pupils widely dilated although reacting to light. The axillary temperature was 36.2 C.; the pulse rate 100, the blood pressure 140/100. Neurologic examination was negative, except for depression in deep tendon reflexes. There were moist rales on auscultation of the lungs. Abdominal examination revealed diffuse tenderness which was more pronounced in both lower

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quadrants. The blood sugar was 640 mg. per 100 ml.; the urine contained 10 per cent glucose and acetone graded 4 plus. The blood nonprotein nitrogen was 210 mg. per 100 ml.; the serum potassium, 2.8 mEq/L; serum inorganic phosphorus, 1.1 mg. per 100 ml.; plasma alkaline phosphatase, 19 Bodansky units; and the serum carbon dioxide combining power, 18 volumes per cent. During the patient's second day in the hospital the electrocardiogram showed evidence of hypopotassemia.

Therapy, with one liter of 3 per cent glucose with 20 units of regular insulin intravenously and 30 units subcutaneously plus 3 gm. of potassium chloride orally, was initiated. Shortly afterwards, the patient showed evidence of circulatory collapse with a systolic blood pressure of 55, the diastolic pressure being unobtainable. Emergency therapeutic measures were adopted, including the administration of sympathol, coramin and ephedrine intramuscularly, and the infusion of 4 liters of 0.9 per cent of sodium chloride intravenously. Insulin administration was discontinued. The Benedict reaction in the urine at that time was still strongly positive. Six hours later, the symptoms of collapse disappeared and blood pressure was 130/90. Subcutaneous injections of insulin were resumed in doses totaling 110 units in 24 hours. Fourteen hours after admission, the patient became more alert, and it was felt that the coma had been brought under control by the next morning.

On January 2, chest x-ray showed partial densities of both apical pleurae with slightly accentuated bronchial tree. A sugar tolerance test done on January 3 showed rise in the blood sugar from 210 fasting to 344 in 60 minutes. On January 4, the fasting blood sugar was 147 and blood nonprotein nitrogen 100. The urine contained 0.5 per cent glucose and no acetone. The dosage of insulin therapy was decreased to 70 units per day subcutaneously. On the sixth hospital day, this was decreased to 60 units given in three doses.

A brief summary of the most important findings during this period appears on Table I.

The patient was discharged on January 13 with a blood sugar of 175, nonprotein nitrogen of 40, serum potassium of 4.6 mEq/L, plasma alkaline phosphatase of 4 Bodansky units, and serum phosphorus of 3.5 mg. per cent. The urine contained 0.4 gm. per cent glucose. Regular insulin, 50 units daily, together with an 1,800 caloric diet containing 100 gm. of carbohydrate, were prescribed. Daily tests for glycosuria were also recommended.

About one month later, on February 19, the fasting blood sugar level was 116 mg. per 100 ml. An electrocardiogram was normal, a glucose tolerance curve was as follows: fasting, 110; after 60 minutes, 192; 120 minutes, 128; and 180 minutes, 110. Insulin therapy was discontinued, while the diet remained unchanged. On March 5, 1951, the fasting blood sugar was 102 and a glucose tolerance test showed the peak of the curve 140 in 60 minutes. A more generous carbohydrate intake

TABLE 1

Significant laboratory data during hospital treatment

Date	Blood sugar mg. per 100 ml. fasting	Nonprotein nitrogen mg. per 100 ml.	Acetonuria	Glycosuria gm. per 100 ml.	Insulin units in 24 hours
Dec. 31	640	210	++++	10.0	110
Jan. 1	380		+++	2.6	110
Jan. 2	333	180	++	1.0	90
Jan. 3	210		+	0.6	70
Jan. 4	147	102	—	0.5	80
Jan. 5	120		—	—	60
Jan. 6	150		—	3.8	30
Jan. 7	178		—	1.2	20
Jan. 8	192	55	—	1.2	20
Jan. 9	172		—	1.0	20
Jan. 10	168		—	0.9	50
Jan. 11	174		—	1.3	50
Jan. 12	183		—	0.6	50
Jan. 13	175	40	—	0.4	50

TABLE 2

Fasting blood sugar values during follow-up studies

Date	June 6 1951	Nov. 9 1951	Jan. 10 1952	May 15 1952	Oct. 4 1952	March 15 1953
Fasting blood sugar (mg. per 100 ml.)	98	110	105	90	95	103

TABLE 3

Glucose tolerance tests during follow-up studies

	Blood sugar, mg. per 100 ml. Minutes after glucose					
	Fasting	30′	60′	90′	120′	180′
Date						
Jan. 3, 1951	210	285	344	338	321	292
Feb. 19, 1951	110	158	192	172	128	110
March 5, 1951	102	158	140	125	105	98
June 6, 1951	98	160	135	130	109	85
Jan. 10, 1952	105	159	137	125	95	109
Oct. 4, 1952	95	162	132	128	98	100
March 15, 1953	103	160	139	128	100	105

was therefore allowed. At subsequent examinations up until March 1953, the patient has been consistently found in excellent condition and the blood sugar level has been normal.

The reports of fasting blood sugar and glucose tolerance tests during the follow-up study of over two years are shown in Tables 2 and 3.

COMMENT

The acute onset of a decreased tolerance for carbohydrate leading to diabetic coma in a patient with no previous personal or family history of diabetes, strongly suggests that this was the result of a massive ingestion of sugar-containing foodstuffs over a short period of time. Since the carbohydrate material was administered in a readily absorbable form, we may assume that it led to a pronounced hyperglycemia, possibly sustained for the period of several days.

Allen[1] and Homans[2] have shown that hydropic degeneration and atrophy of the pancreatic islet tissue is associated with hyperglycemia. Jacobs and Colwell[3] found severe pancreatic lesions in dogs given a constant infusion of glucose intravenously. The survival time was directly related to the dose given and death was preceded by a syndrome characterized by hyperglycemia, glycosuria and acidosis. Woerner[4] observed degranulation and hydropic degeneration of the beta cells in guinea pigs administered large doses of glucose intravenously. Gomori et al.[5] reported that degranulation of the beta cells occurred when hyperglycemia was induced by a single intraperitoneal injection of dextrose. The lesion was reversed when blood sugar returned to normal levels. Ingle[6a,b], in rats force-fed a high carbohydrate diet until death, noticed that the animals became glycosuric when the intake surpassed a certain limit.

Dohan and Lukens[7] administered massive doses of glucose intraperitoneally to normal and partially pancreatectomized cats. Ten animals developed hydropic degeneration of the beta cells, and three of this group, one normal and two partially depancreatized, remained permanently diabetic after the end of the treatment. The recent observations made by Peterson[8] further demonstrate the close relationship between blood sugar level and pancreatic islet cells. Intracardiac injection of a single massive dose of glucose in rats caused within 15 minutes a marked degranulation of the beta cells, the complete recovery of which was not observed until 48 hours later. Fasting blood sugar levels were found elevated at 24 hours and glucose tolerance curves were of the diabetic or potentially diabetic type. Thereafter, while fasting hyperglycemia disappeared at 48 hours, glucose tolerance remained impaired for a week, at the end of which time it returned to normal. In one rat, treated with repeated injections of the small dose of glucose, a temporary diabetic state, with hyperglycemia and glycosuria lasting several days, was observed.

Barron and State[9] have administered dextrose in a continuous infusion to dogs over a period of four to nine days and have found complete degranulation of the beta cells in all the animals.

The preceding experimental data show that degranulation and hydropic degeneration of the islands of Langerhans are asscoiated with prolonged hyperglycemia. On the other hand if the high blood sugar level is lowered by insulin[10,11], phlorizin[12], diminished dietary intake, or adrenalectomy, the normal pattern of the islet cells is restored[13]. The mechanism by which this damage is produced remains an unanswered question. Lazarow has suggested[14] that the excessive demand for insulin would cause an increase of the rate of insulin synthesis, and thus a depletion of insulin precursors. At any rate it appears that the excessive demand of insulin leads to exhaustion of the islet cells, and, if hyperglycemia persists, to degeneration.

As far as the development of human diabetes is concerned, the role of hyperglycemia is causing degranulation and hydropic degeneration of the beta cells is still a matter of controversy[15]. The alterations described from autopsy material do not help in solving the problem. On the other hand Bell[16a,b] has recently found, by means of a new staining technic[17], a high incidence of beta cell degranulation in diabetic persons, which closely resembles that found in the rat, the cat and in the dog after substained provoked hyperglycemia. Lukens[13] suggests that degranulation of the beta cells may be a common denominator indicating hyperglycemia which may also play a role in human diabetes, at least in the early stages of the disease. Duncan[18] points out that hydropic degeneration, which follows degranulation of the beta cells, is an acute and transitory lesion. Therefore, it can only be detected early in the disease, shortly after the onset of clinical manifestations, or during the progression of fulminating diabetes.

Regarding the possible role that the infection suffered by the patient a few days before the onset of diabetic acidosis and coma played in the etiology of the syndrome, it is interesting to note that either the diabetic or the nondiabetic may show, during infections, a lowered tolerance for carbohydrate. Labbé[19] found in cases of pneumonia such a decreased tolerance, and Root and Warren[20] have reported that both insular necrosis and regeneration may occur during the course

of this disease. Furthermore it is possible that the stress accompanying infection led to an overproduction of adrenal steroids of the gluconeogenic type, thus favoring the appearance of diabetes. Indeed such a mechanism has been postulated by Albright[21] in cases of diabetes following stress and more recently by Gordon[22]. Evans and Butterfield[23], and Levenson[24] have observed hyperglycemia, glycosuria and polyuria in severely burned patients given high caloric diets. Ingle et al[25–26] have shown that the administration of moderate doses of adrenal steroid hormones and high carbohydrate diet to the partially depancreatized rat cause the appearance of hyperglycemia and glycosuria; also, high doses of cortisone and adrenocorticotropin[27, 28] administered to the intact rat, given a high fat or moderate carbohydrate diet, determine the appearance of glycosuria and acetonuria. Cavallero and Malandra[29] have emphasized the role of latent pancreatic islet deficiency in facilitating the diabetogenic effect of cortisone, and have also demonstrated that the latter further aggravated pre-existing diabetes produced by alloxan or total pancreatectomy.

On the other hand a discharge of adrenal cortical hormones may occur following a high intake of carbohydrate, as it has been suggested by Elmadjian et al[30], who have found a significant lymphocytopenia in intact rats treated with high doses of sugar.

Thus, it can be briefly stated, according to Joslin et al[31] that infection may interfere with carbohydrate metabolism by: (a) lessening the production of insulin; (b) decreasing the production of hormonal antagonists; (c) causing the destruction of insulin; and (d) reducing the storage of glycogen in the liver. The direct role of infections in the etiology of diabetes, however, has been considered of slight importance[32], although there seems to be no doubt that they intensify the severity of existing diabetes or that they may make evident previously undetected diabetes. Even though the administration of carbohydrate in our patient was begun when the clinical and functional picture of pneumonia had disappeared, the possibility still remains that as a consequence of infection, the functional adequacy of the pancreatic island tissue was impaired to such a degree that it was incapable of responding to an excessive load of carbohydrate.

In conclusion, we feel that the diabetic coma syndrome presented by this patient was the result of a sudden excessive demand of insulin imposed upon an island cell tissue already impaired by a recent infectious episode, and persisting until it led to an eventual insulin deficiency. The administration of exogenous insulin together with the adjuvant therapy led to a recovery which was complete at the end of six weeks. Unfortunately, there were no blood sugar values available prior to the patient's hospital admission, but the fact that in follow-up studies of over two years the patient showed a normal carbohydrate tolerance lends support to the hypothesis of a transient exhaustion of the insular tissue as the primary etiologic factor.

SUMMARY

A case of transient diabetes leading to coma in a 62-year-old man with no previous personal or family history of diabetes, following an excessive intake of carbohydrate over a short period of time, is reported. Treatment with diet and insulin resulted in complete recovery. Follow-up studies of three years' duration have shown this patient's fasting blood sugar levels and glucose tolerance curves to be persistently normal.

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Key to Chronic Disease Control

The opening of the Clinical Center symbolizes the hope and faith of the American people that the major killing and crippling diseases of this century ultimately will be conquered.

The very nature of these diseases—subtle reactions of the human organism to its biological inheritance, its total environment—makes it clear that clinical and laboratory research will play an increasingly significant role in medical and public health progress for many years to come.

In a sense, we have reached a period of consolidation of forces for a broad attack on chronic diseases—an attack that can be fully successful only after years of intensive research. This means that we must not only press the search for new knowledge, but we must also use what we do know more intensively, more effectively.

The key to chronic disease control today is early diagnosis and treatment. The first great promise of medical research is to find new and more efficient ways to early diagnosis and treatment. And the second is ultimately to discover means of positive prevention.

From extracts from remarks of Surgeon General of the Public Health Service at the dedication of the Clinical Center, by Leonard A. Scheele, M.D., in Public Health Reports, September 1953

Extreme Insulin Resistance in Diabetic Coma

Report of a Fatal Case of Juvenile Diabetes Treated with 7,555 Units of Insulin in 45 Hours

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Large amounts of insulin are frequently necessary in the treatment of advanced diabetic acidosis. Glass[7] has described administration of 2,795 units and Weiner[21] of 3,250 units in 24 hours. We feel that a fatal case of juvenile diabetes with acidosis and coma, in which reduction of blood glucose from 776 to 186 mg. per cent occurred only after administration of 7,555 units of insulin over a 45-hour period, is unusual enough to merit a short report.

The patient was a well developed, poorly nourished nine-year-old white boy. The past history was not remarkable except for an episode of prolonged pneumonitis one year before the onset of the present illness. In March, 1952, the patient was seen in the office of one of us (Doctor Picard) for a "check-up." At that time, the examination, which included urinalysis, was essentially negative. Shortly thereafter, the boy, who had always been a poor eater, developed an excellent appetite. The parents, in their pleasure at the change, overlooked the accompanying weight loss, polydipsia and polyuria; the existence of these symptoms was brought out later only by close questioning.

Two days before admission to the hospital the patient first complained of severe abdominal pain and then became lethargic. He vomited repeatedly. By the time medical attention was sought, on April 6, 1952, he was stuporous; he had a slight fever, and he showed signs of abdominal tenderness and dehydration. He was hospitalized immediately.

His temperature on admission, taken rectally, was 99.2 degrees. The pulse was reported as "rapid"; the blood pressure was 90/60 and the respiration was rapid and shallow. Palpation of the abdomen caused the patient to moan and some rigidity was noted, especially over the right lower quadrant. No masses were palpable.

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The reports of laboratory tests were as follows: red blood count, 4,470,000; hemoglobin, 13 gm.; white blood count, 34,900, with 87 per cent polymorphonuclear leucocytes. Roentgenograms of the chest and abdomen were essentially negative.

A peculiar set of circumstances tragically delayed the diagnosis by almost a day. Because a negative urinalysis had been obtained two weeks previously and because of the misleading combination of abdominal symptoms and signs with high leucocytosis at the time of admission, the possibility of diabetic acidosis was not considered. In addition, the patient entered the hospital at noon on a Sunday and the "routine" urine specimen was set aside until the next morning.

The boy was given 200,000 units of aqueous penicillin on admission, again in two hours and 100,000 units every three hours thereafter. A slow intravenous infusion of 5 per cent glucose in normal saline was begun.

His condition deteriorated during the night. By five o'clock the next morning, his temperature, after rising to 104.2 degrees rectally, had fallen to 100.8 degrees. He was cyanotic and pulseless; the blood pressure was unobtainable. His extremities were cold. The respiration consisted of shallow gasps. The examination of the abdomen revealed the previously noted slight rigidity. Significantly, his eyeballs were discovered to be extremely soft.

The chart was then reviewed and the absence of a report of urinalysis became apparent. A urine specimen was obtained; it contained more than 2 per cent sugar, the test for acetone was strongly positive. Blood samples were drawn for determination of sugar and carbon dioxide combining power; these were later reported as 776 mg. per 100 cc. and 22.4 volumes per cent.

Once the diagnosis of coma had been established, immediate attempts were made to overcome the dehydration, restore electrolyte balance and correct the hyperglycemia. Fluids given parenterally included normal

saline, sixth molar sodium lactate and 2500 cc. of 5 per cent dextrose. Almost all of the insulin was given intravenously. Determinations of the blood sugar, carbon dioxide combining power, urine sugar (graded 1 to 4 plus) and insulin dosages are charted in detail in Figure 1. At noon the patient received 40 mEq. of potassium (as potassium chloride) intravenously and 120 mEq. by gavage.

Two hours after definitive treatment was begun, the patient was distinctly better. The blood pressure had risen to 60/40. The extremities were warmer and the pulse was stronger and slower. He began to respond to questioning. However, progress halted at this point.

By the morning of April 7, in view of the rise in the blood sugar level, it was apparent that the substantial quantities of insulin this 25.4 kg. child had received so far had been without significant effect and that the moderate improvement noted had been due to other factors. As still larger doses failed to control glycosuria, hyperglycemia actually mounted and the shock state

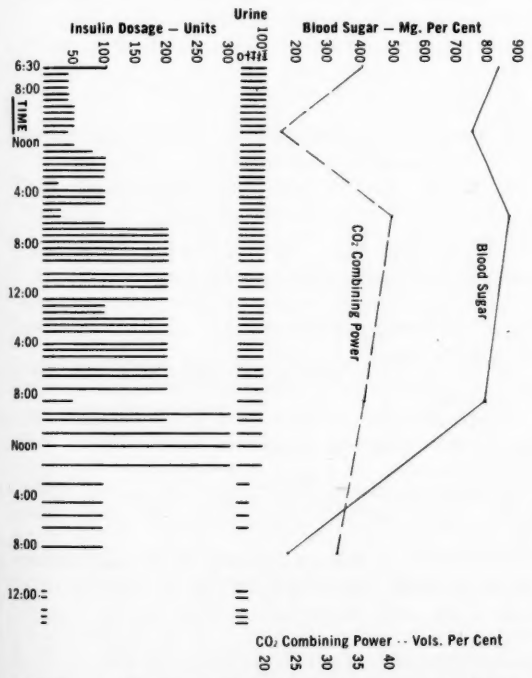

FIGURE 1 Laboratory and treatment data for the 45-hour period from diagnosis of diabetic acidosis with coma to death of the patient. Solid line graph: blood glucose (mg. per 100 cc.), interrupted line graph: carbon dioxide combining power (volumes per cent), upper bar graph: urine sugar (graded 1 to 4 plus), lower bar graph: individual doses of regular insulin (units). Abscissa: time in hours.

persisted, we felt that the time had come to disregard textbook dosage schedules. From then on, until the blood sugar began to fall and at the same time progressive oliguria interfered with urine sugar determinations, the patient received increasingly greater amounts of regular insulin.

The blood urea nitrogen at 8 a.m. on April 8 was 76 mgm. per 100 cc. By midafternoon of that day, the urinary output had begun to fail. At 11:20 a.m. the same day, the first reduction in glycosuria was found. Subsequent urine specimens showed no more than "2 plus" sugar. The insulin dosage was accordingly reduced. By 8 p.m. the blood sugar level was 186 mg. per 100 cc. However, the oliguria increased and the coma deepened. Despite the use of stimulants, the pulse and blood pressure again disappeared. At 2:20 a.m., April 9, the patient expired.

An autopsy was performed. The liver showed areas of parenchymatous degeneration. Gross and microscopic examination of the pancreas, suprarenals and muscle tissue (H. and E. stain) failed to demonstrate significant changes in these organs. Permission to examine the brain could not be obtained.

DISCUSSION

Insulin resistance has been attributed to many factors. Acidosis[1, 3–21] uniformly increases insulin requirements. Infection[3, 10, 11] with its attendant "alarm reaction"[10, 14, 15, 18] is a common cause of increased need for this hormone. Liver disease[4, 10], hyperfunction of the thyroid, anterior pituitary and adrenal cortex[5, 6, 10], allergy[4] and delayed activation of insulin[8] have all been implicated.

The present report deals with a patient who was moribund when treatment was begun. Prolonged, severe acidosis and terminal changes in metabolism appear to be the major factors involved in this case. Although the pituitary could not be examined, gross and microscopic study of other tissues revealed no disease states which might have contributed to insulin resistance. Since the child received almost all his insulin by the intravenous route, poor absorption could not have been a factor.

The patient did not die in extreme hyperglycemia; the final blood sugar level, six and a half hours antemortem, was only 186 mg. per 100 cc. While it may be argued that the fall in blood glucose was a terminal phenomenon and unrelated to insulin administration, such a fall is not usual in untreated diabetic acidosis. A cause and effect relationship between cumalative insulin dosage and the eventual drop in blood sugar is more probable.

The administration of glucose solutions during treatment of diabetic acidosis is not without disadvantages, one of which is interference with evaluation of the response to insulin. Two reasons prompted the use of 5 per cent glucose in this case. First, it seemed undesirable to give the large amount of fluid required entirely as sodium containing solution because of possible adverse effects on cardiorenal dynamics. Second, it was thought that the total amount of glucose available for metabolism was actually low: in spite of the marked hyperglycemia, it was estimated that the amount of glucose in the extracellular fluids was less than 40 gm.

Significant hypokaliemia was assumed to be present when characteristic changes were found in the first electrocardiogram[2]. Since hypopotassemia, when associated with diabetic acidosis, may delay recovery from the latter condition or even lead to death, prompt corrective measures were deemed necessary. A flame photometer was not then available; because of the desperate condition of the patient we decided to estimate serum potassium status by comparison of serial electrocardiograms rather than to rely on time-consuming chemical determinations. A marked return toward a normal curve was noted in tracings which were obtained after potassium ion had been supplied.

The dangers inherent in the use of such large doses of insulin were fully appreciated, but at the same time the need for heroic measures was obvious.

Although the primary objectives of re-expansion of the extracellular fluid volume, restoration of electrolyte balance and reduction of hyperglycemia seem to have been substantially attained, the success achieved was chemical only and too late to prevent the death of this boy in shock, anuria and azotemia.

SUMMARY

A fatal case of juvenile diabetes, with acidosis and coma, is described in which reduction of blood glucose from 776 to 186 mg. per 100 cc. occurred only after administration of 7,555 units of insulin over a 45-hour period.

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The Metabolism of Fructose by the Extrahepatic Tissues

Arne N. Wick, Ph.D., James W. Sherrill, M.D., and Douglas R. Drury, M.D., La Jolla, Calif.

Minkowski[1] in 1893 proposed fructose as a metabolic fuel on the basis of his observations in experimental diabetes. Bollman and Mann[2] in 1934 made a study of fructose metabolism in depancreatized dogs and found that it was utilized better than glucose at first, but that this difference lasted only five days, and thereafter the same amounts of sugar were lost in the urine after feeding the same amounts of the two sugars.

This suggests that fructose might at first be stored more readily as glycogen in the liver but that after five days this storage capacity would be saturated. The difference in the behavior of the two hexoses would result then from a better storage of fructose as glycogen by the liver[3], which would be a temporary matter and have little effect on the ultimate combustion of the sugars. According to this view, fructose need not be oxidized directly by the tissues but only after conversion to glycogen or glucose. However, Chernick and Chaikoff[4] have presented evidence indicating that the liver can oxidize fructose without transforming it first to glucose. This is based on their observation that in slices of liver from diabetic rats, oxidation of glucose to carbon dioxide is markedly depressed, whereas the oxidation capacity for fructose is the same as in normal animals.

There is much to support the view that the extrahepatic tissues also may oxidize fructose directly. After fructose administration, the R. Q. rises more quickly than with glucose, suggesting that it is more rapidly oxidized[5]. With fructose, an R. Q. of one is soon reached, and it seems doubtful that such a large metabolic change could be due to the liver alone. On the basis of femoral arterio-venous differences, Weinstein & Roe[6] conclude that fructose is utilized directly by muscle. Several papers have appeared recently which report a greater utilization of fructose than of glucose in diabetic patients. The authors conclude that the metabolism of fructose differs from that of glucose and that in the diabetic the metabolism of fructose by liver and muscles is not depressed as is that of glucose[7]. This is supported by the finding that in muscle as well as in liver there is a specific kinase for fructose which differs from that for glucose[8]. On the basis of this work the administration of fructose has been proposed as a source of fuel under conditions in which glucose utilization is retarded. Advocates of this procedure generally assume that the extrahepatic tissues are able to utilize fructose readily.

The claim that fructose can be metabolized by the extrahepatic tissues should be examined experimentally. To do this, the liver must be removed and the metabolism of fructose by the extrahepatic tissues studied directly. We have done so by following the disposal of labeled fructose administered to eviscerated rabbits. We measured its rate of disappearance from the blood and the rate of oxidation to carbon dioxide. In addition, we determined the effect of insulin on these factors.

We also studied the effect of fructose on the oxidation of glucose. Fuels that are readily metabolized will displace glucose as a source of fuel in combustion[9] and, if fructose were rapidly taken up by the oxidative enzyme systems, it might substitute for glucose if administered to the animal. We investigated this with the aid of labeled glucose. The animals were kept under maximal insulin activity and maintained with the C^{14} labeled glucose until the activity of the expired carbon dioxide leveled off, indicating a fairly constant rate of oxidation of glucose. Inactive fructose was then given to the animal with other factors kept as before, and the effect of the superimposed fructose on the rate of glucose oxidation was then determined.

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Address communications to Doctor Wick, Scripps Metabolic Clinic.

METHODS

The general plan of the experiments is similar to those reported before and described in previous papers[10, 11]. Non-fasted rabbits were used. The animals were eviscerated, including the kidneys, under ether anesthesia. A tracheal cannula was inserted at the time of the operation in order to facilitate the collection of the expired carbon dioxide for radioactivity determination. The C^{14} labeled glucose and fructose were uniformly labeled and prepared by biosynthesis. When insulin* was given, it was injected intravenously in amounts to give maximum action (20 units per hour).

MEASUREMENT OF BLOOD FRUCTOSE DISAPPEARANCE AND OXIDATION RATE

After recovery from the anesthetic, the animals were injected intravenously with a known quantity of radioactive fructose. Carrier fructose was added in some of the experiments. Samples of plasma were taken one-half or one hour after the fructose injection in order to calculate the primary volume of distribution. Other samples were taken at later periods for determining the blood disappearance rate from changes in the dilution of the radioactivity. The total radioactivity per unit volume of plasma was measured as follows[12]: The plasma was mixed with an equal amount of acid phosphate buffer, frozen, and lyophilized. Aliquots of the dried plasma were used for radioactivity determinations. The distribution of fructose was calculated by taking the total counts injected after correcting for the small amount oxidized and dividing by the radioactivity per milliliter of plasma. The expired carbon dioxide was collected and precipitated as barium carbonate for radioactivity determinations.

THE EFFECT OF FRUCTOSE ADMINISTRATION ON GLUCOSE OXIDATION

After recovery from the evisceration the animals were maintained for four hours under maximum insulin activity with enough radioactive glucose to maintain a normal blood sugar level. Throughout the run the specific activity of the circulating glucose was kept at a constant level[10]. At the end of the fourth hour the unlabeled fructose was superimposed on the glucose and insulin injections, and the experiment was continued for another three hours. By following the radioactivity of the expired carbon dioxide, any changes in glucose oxidation produced by the injected fructose can be determined. This procedure has been used in studying the metabolism of acetate[13] and beta-hydroxybutyric acid[9]. By starting the fructose injection at the beginning of the fifth hour, each animal acts as its own

*The insulin used in this work was contributed by the Lilly Research Laboratories.

RESULTS

The volumes of distribution of fructose are shown in Figure 1. It is seen that insulin has no measurable effect on the body distribution even after 6 hours of maximum action. It should be pointed out that labeled compounds are especially useful for studying their volume of distribution with and without insulin action, particularly in those experiments in which only trace amounts of material are administered. If the rate of cell penetration is low and large amounts of carrier are administered, the extent of cell penetration (transfer rate) may not be readily measurable. On the other hand, a low rate of cell penetration can be easily measured when giving trace amounts (1-10 mg. per kilo) of the labeled test compound. Obviously both types of experiments must be carried out since cell penetration in some cases may be directly related to the plasma concentration of the test substance. In the experiments reported here with labeled fructose and insulin, the volume of distribution of fructose after giving either trace amounts of the sugar (Experiments 1 and 2) or large amounts still gave distribution values equivalent to 16-24 per cent of the body weight which corresponds to the extracellular compartment. It is apparent from these results that the transfer rate of fructose (that is, the transfer of fructose from the extracellular to the intracellular compartments) is very low despite the action of insulin.

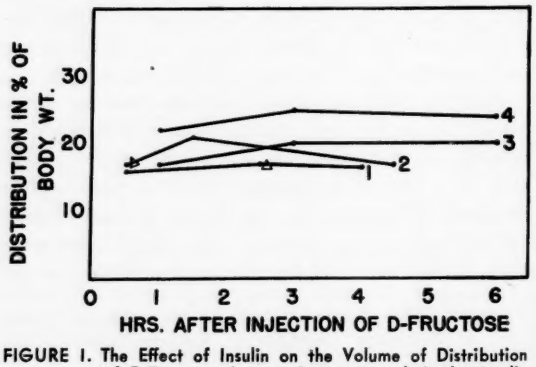

FIGURE 1. The Effect of Insulin on the Volume of Distribution of D-Fructose. In experiments 3 and 4, the insulin was given at zero hour. In experiments 1 and 2, at the time indicated by the triangle. In experiments 3 and 4, the radioactive fructose was given with carrier fructose equivalent to 1 gm. per kgm. of animal weight. In experiments 1 and 2, no carrier fructose was administered.

In Figure 2 are the oxidation values of fructose obtained after the administration of a single dose equivalent to 1 gm. per kgm. of body weight. These results with fructose represent the average of four experiments—two with insulin injections and two without. It is seen that less than 5 per cent of the total metabolism can be accounted for by fructose oxidation either with or without insulin administration. This low rate of fructose oxidation is equivalent to an oxidation of 5 to 20 mg. per kgm. which is about one tenth of that obtained for glucose. Data obtained with glucose from previous experiments[10, 11] under comparable conditions are included for comparison purposes. It is apparent that fructose, unlike glucose, does not respond to insulin action.

In Table I are the oxidation values obtained by superimposing non-labeled fructose on the radioactive glucose and insulin at the beginning of the fifth hour. It is apparent that fructose does not depress the rate of glucose oxidation in the presence of insulin, and it is concluded that glucose is metabolized, in preference to fructose, by these tissues. Results for control animals have been given in several previous papers[9, 14].

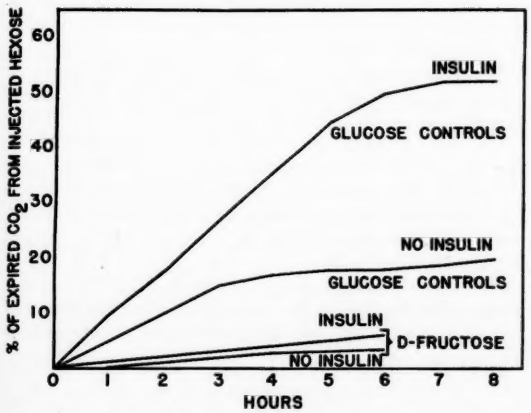

FIGURE 2. The Relative Participation of Fructose and Glucose in Total Metabolism.

TABLE 1

The effect of fructose on the metabolism of glucose in eviscerated animals treated with insulin

		Exp. 5	Exp. 6
Per cent of expired CO_2 from injected glucose	1st hr.	7	—
	2nd hr.	14	17
	3rd hr.	22	23
	4th hr.	31	30
	5th hr.	36	36
	6th hr.	39	37
	7th hr.	38	44
Fructose injected.* Mg/kg/hr.		370	350
Animal Wt. (kilos)		1.60	1.18

*A priming dose equal to the hourly injection rate was given at the start of the fructose injections.

DISCUSSION

Our results indicate that fructose distributes readily in a volume equivalent to 20-25 per cent of the body weight. This is the volume of the extracellular compartment. There is very little passage of fructose from this space into the intracellular compartment even over a six-hour period. Insulin does not accelerate this transfer as it does that of glucose and galactose[12]. Fructose is then like sorbitol[15] in that it remains in the extracellular compartment and enters the cells to a very small extent.

In support of the view that fructose differs from glucose in not entering the extrahepatic cells is the low rate of oxidation of fructose. Before a fuel could be oxidized in the body, it would have to get inside the cells since the extracellular fluid has no capacity to carry on oxidative reactions. The small rate of fructose oxidation may result from a very low rate of penetration into the cells. On the other hand, even this small amount of fructose oxidation may not be the result of direct combustion of this hexose. With the liver and kidneys removed, there is little likelihood of its conversion to glucose. However, there is the probability of considerable conversion of fructose to lactic acid. This takes place at quite a high rate in the blood, and it is likely that a considerable fraction of the fructose is tranformed to lactic acid. This latter substance is readily oxidized by the extrahepatic tissues[16]. The continued rise in activity of expired carbon dioxide could be due to a gradual increase in labeled lactate coming from fructose.

Our results indicate fructose has limited use in conditions such as diabetes where glucose utilization by the extrahepatic tissues is impaired. In the intact animal the chief effects of fructose administration would be its oxidation by the liver and an increased deposition of liver glycogen. However, without insulin the extrahepatic tissues use little glucose[11]. This deficiency still remains a serious defect in diabetes and fructose will not remedy it.

SUMMARY

The metabolism of d-fructose has been studied in

eviscerated-nephrectomized rabbits with the following results:

1. Fructose distributes in a volume equivalent to the extracellular compartment with very little transfer into the intracellular compartment with time. Maximum insulin action even over a six-hour period does not accelerate the fructose transfer.

2. The low rate of fructose transfer is reflected in an equally low rate of fructose oxidation. Less than 5 per cent of the total metabolism can be accounted for by fructose oxidation with or without insulin administration.

3. Superimposing fructose on glucose injections in insulin-treated animals does not depress glucose oxidation. Thus, glucose in the presence of insulin is oxidized in preference to fructose.

It is concluded that the low rate of fructose oxidation observed in these experiments is due to the inability of fructose to enter into the cells of the extrahepatic tissues; the utilization observed in intact animals must be due to liver action.

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Group Instruction in Weight Control

Ten overweight women in Alexandria, Va., who participated in group conferences on weight control, lost an average of 17.8 pounds each over a 20-week period. The entire class lost an average of 42.7 per cent in excess weight, ranging from 13.5 to 131.5 per cent. Weekly conferences were held between March 29 and August 25, 1952, at the Alexandria City Health Department.

Free discussion, centering first on nutritional and psychological orientation and later on self-analysis, was the guiding principle of the conferences. Losing a pound a week until the ideal weight was approximated was selected as each participant's arbitrary goal.

It was repeatedly emphasized that medical supervision of the group members was the sole responsibility of their own physicians. The group leader conducted the conference in such a way that the women would be motivated to decrease their caloric intake. Loyalty in attendance was stressed more than weight loss because it was believed that continued attendance eventually would bring about sufficient motivation to achieve weight reduction.

From *An Experiment with Group Conferences for Weight Reduction,* by A. L. Chapman, M.D., in Public Health Reports, April, 1953.

ABSTRACTS

Acevedo, Dario; and Migone, Alfieri (*Lima, Peru*): DIABETES AND EXPERIMENTAL ESTROGENS. Anales de la Facultad de medicina 35:261-83, 1952.

This paper deals with the results of the authors' investigation on the action of estrogens in experimental diabetes and points out the probable mechanism of their antidiabetic effect. Pancreatectomized animals under estrogen therapy are somewhat similar to Houssay animals. There is (a) a disappearance of the hyperglycemia, (b) an absence of glucose and ketone bodies in the urine, (c) less malnutrition and greater survival rate than in test dogs, and (d) greater appetite and a better general condition. Hypoglycemic crises are aggravated by fasting or hypoalimentation. The mechanism of the antidiabetogenic action of estrogens is not well understood. It is necessary to remember that such hormones in high and prolonged doses are capable of producing morphologic and functional changes in the endocrine glands and other organs.

Adams, Theodore W.; Whitely, James M.; and Parrott, Max H. (*Portland, Ore.*): INTRAUTERINE ROENTGENOGRAPHY AS AN AID IN DETERMINING FETAL AGE. A PRELIMINARY REPORT. West. J. Surg. 61:448-52, August 1953.

The authors report their technic and results in visualizing by roentgenography the distal femoral epiphysis of the fetus as an aid to determining fetal age. In a small number of cases there was no fetal mortality when the distal femoral epiphysis was observed prior to delivery. Of four babies delivered before the appearance of a distal femoral epiphysis, three died, prematurity being the cause of death of two. Postdelivery x-rays compared well with the predelivery x-rays, which indicates that the technic is feasible. The authors feel that this method of determining fetal age is promising.

Addison, Vesta E.; Tuttle, W. W., Daum, Kate; and Larsen, Rosemary (*Coll. of Med., State Univ. of Iowa, Iowa City, Iowa*): EFFECT OF AMOUNT AND TYPE OF PROTEIN IN BREAKFASTS ON BLOOD SUGAR LEVELS. J. Am. Dietetic A. 29:674, July 1953.

Data were collected from a group of fourteen normal women between the ages of twenty and thirty-seven years relative to the effect of the source and amount of protein in breakfast on the maintenance of the blood sugar level following the meal. The data suggest that 15 gm. protein in breakfast is on the border line with respect to maintaining the blood sugar at or above the fasting level for 3½ hrs. after the meal. Whether the protein is of plant or animal in origin seems to be of no consequence.

Alexander, Richard I. (*Victoria Infirmary, Glasgow, Scotland*): FATAL HYPOGLYCAEMIA IN A DIABETIC PATIENT WITH PITUITARY NECROSIS. British Medical Journal 1:1416-18, June 27, 1953.

Another case of pituitary insufficiency in a diabetic is reported. Extended hypoglycemia as the ultimate cause of death is discussed.

Altschule, Mark D.; Grunebaum, Henry U.; Parkhurst, Barbara H.; and Siegel, Elaine P. (*Lab. of Clinical Physiol., McLean Hosp., Waverley, Mass., and Dept. of Med., Harvard Med. Sch., Boston, Mass.*): MOBILIZATION OF GLUCOSE BY PHLORIZIN IN PATIENTS WITH MENTAL DISORDERS. Arch. Neurol. & Psychiat. 70:235-39, August 1953.

Changes in carbohydrate metabolism after injection of phlorizin were studied in patients with mental disease before and after treatment. The amount of glucose excreted was in the normal range. However, changes in blood sugar level during the test indicate that mobilization of carbohydrate is sluggish in some patients; this abnormality apparently involves processes other than epinephrine-induced hepatic glycogenolysis.

Anderson, E. E.; Esselen, W. B.; and Fellers, C. R. (*Dept. of Food Technol., Univ. of Massachusetts, Amherst, Mass.*): NONCALORIC SWEETENERS IN CANNED FRUITS. J. Am. Dietet. A. 29:770-73, August 1953.

There was little difference in the acceptability of canned peaches, pears, blueberries, raspberries, sweet cherries and

rhubarb sweetened with either sucrose, Sucaryl sodium or saccharin. In all examinations, the various sweetened packs were unanimously chosen as more desirable than the water-packed fruit.

Anderson, George E. (*Dept. of Med. of The Brooklyn Hosp. and the State Univ., Coll. of Med., New York*): THE USE OF THE ISOCALORIC DIET IN THE MANAGEMENT OF DIABETES MELLITUS. Brooklyn Hosp. J. *10*:201-20, October-December 1952.

Hyperglycemia can be made to serve a constructive physiologic purpose in the diabetic patient, provided it is not unrelenting in character but is short-lived, with prompt recovery. Then it parallels the "rolling hills" of normoglycemia, even if at a relatively higher level; and then once again, as in normal individuals, it becomes a stimulus to the patient's own native intrinsic insulinogenic or insulin-effectuating function. The diabetic patients with relative insufficiency of insulin, comprising the large majority of obese adult diabetics, are characteristically rather insensitive to insulin, as this can be measured by glucose-insulin tolerance tests. The patient's responsiveness to insulin, also intrinsic, can be built up by progressive increases in carbohydrate ingested, provided always that the calorigenic value of his total dietary intake is maintained constant and close to his basal needs. By a simple system of isocaloric diet-prescription, this can be accomplished clinically with facility. The juvenile type of diabetic (young or old) characteristically suffers predominantly from an absolute insulin-insufficiency. He must, therefore, always have insulin, but he is usually sensitive (or over-responsive) to insulin. High-carbohydrate, low-fat diet in such a patient will not infrequently convert him into the so-called "brittle" type of diabetic. For ideal therapeutic results, he should accordingly be given a relatively nonstimulating or, at best, an only mildly stimulating type of diet. His dietary needs are also easily met by use of the isocaloric system of diet-prescription. Finally, blind treatment of hyperglycemia as an end in itself rather than as a means to an end may be unphysiologic. Favorable clinical results arising therefrom are usually fortuitious rather than reasonably predictable. Excessive insulin-substitutional treatment in lieu of native insulinogenic function is clinically tantamount to "hormonal pancreatectomy" and should therefore be shunned whenever it is possible to build up the patient's own intrinsic insulin-producing mechanism. Unrelenting hyperglycemia must be broken, since only thereby can there be re-established a suitable physical substrate for normal resumption of a trigger mechanism of stimulation of the intrinsic insulinogenic or insulin-effectuating mechanism through the agency of ingested carbohydrate.

Ashby, D. W.; and Tweedy, P. S. (*Gateshead and Bensham Genl. Hospitals, England*): FRIEDREICH'S ATAXIA COMBINED WITH DIABETES MELLITUS IN SISTERS. British Medical Journal *1*:1418-21, June 27, 1953.

Cases of Friedreich's ataxia and diabetes occurring in siblings are described; the previous literature is reviewed; and theories of causation are discussed.

AZAR, GEORGE (*Baton Rouge, La.*): SURGERY IN DIABETES. New Orleans M. & S. J. *104*:665-67, October 1952.

A determined effort should be made to stabilize the diabetic state, to correct the fluid and electrolyte balance, combat anemia and hypoproteinemia, if present, and to replenish the blood volume before elective surgery is done. In acute abdominal conditions this evaluation may not be possible due to existing circumstances, and in these cases, it seems wiser to operate and treat the diabetes later.

Lumbar sympathetic block with procaine and lumbar sympathectomy are methods of salvaging in some instances a part of a limb that would otherwise be sacrificed and are worthy of consideration. In general, it may be stated that, though the mortality rate for surgery remains higher in the diabetic than in the nondiabetic for comparable conditions, surgical operations on the patient can be undertaken with a reasonable assurance of safety, provided all of the preoperative requisites are satisfactorily met and the postoperative therapy is adequate.

Bacchus, Habeeb; and Heiffer, Melvin H. (*Dept. of Physiol., George Washington Univ. Sch. of Med., Washington, D. C.*): INFLUENCE OF ASCORBIC ACID ON THE METABOLIC ACTIONS OF CORTICAL HORMONES: CARBOHYDRATE METABOLISM. Am. J. Physiol. *172*:276-80, February 1953.

Insulin tolerance tests were conducted on adrenalectomized and adrenal-demedullated rats in experiments designed to test the influence of ascorbic acid on the actions of cortical hormones on carbohydrate metabolism. In addition, the urinary glucose and nitrogen were stud-

ied in adrenalectomized-phloridzinized animals for the above purpose. The data indicate that ascorbic acid enhances the insulin tolerance of cortisone-treated, adrenalectomized rats, and of corticotrophin-treated, adrenaldemedullated rats. The vitamin by itself does not affect insulin tolerance. The urinary glucose-nitrogen studies indicate that an increase in urinary glucose and nitrogen follow the injection of cortisone. These increases are enhanced when ascorbic acid is used along with cortisone. The data in view of previous work suggest that the vitamin enhances the liver glycogen depositing ability of cortisone and are interpreted to suggest that the vitamin enhances the gluconeogenic actions of cortical hormone.

Bahner, F. W. R.; and Taylor, N. R. W. (*Med. Res. Council's Clin. Endocrinology Res. Unit, Dept. of Pharmacol., Univ. of Edinburgh, Scotland*): FASTING KETOSIS IN HYPOPHYSECTOMISED AND NORMAL RATS. Quart. J. Exper. Physiol. 37:221-23, December 1952.

Hypophysectomy caused a significant delay in the accumulation of acetoacetic acid in the blood of rats during a fast, but did not affect the final concentration.

Bartelheimer, Heinrich (*Berlin City Hosp.*): PATHOGENIC AND CLINICAL DIABETES QUESTIONS. Klinische Woschenschrift *31*:345-50, April 15, 1953.

In order to study the pathogenesis of diabetes, the author investigated pregnancy in alloxan-diabetic rats. In a series of experiments, alloxan was given to the animals only after acutal conception. Interesting deviations showed up in the progeny. There occurred incidences of macerated fetuses and development of malformations—changes corresponding to those in humans. But most of all, giant animals of the male sex were observed which attained almost double the body weight of animals of the same breed. Here the birth weight was not conspicuous. The abnormal growth tendency became apparent only several weeks later. In this time, there occurred also a passing hyperglycemia and glycosuria.

Benard, H.; Cruz-Horn, A.; Kaswin, A.; and Seeman, A. (*Paris*): ABSENCE OF MODERATING ACTION OF INSULIN WITH REGARD TO HEPATIC GLYCOGENOLYSIS. Comptes rendus des séances de la Société de biologie *146*:417-18, March 1952.

The insulin preparations, used in varying doses of 5 to 25 units, were devoid of the "hyperglycemic factor" which often contaminates insulin proper and which could have concealed a possibly moderating action of the latter with regard to glycogenolysis. The negative experiments reported do not contradict a glycogenopexis action of insulin but lead to the assumption that this action can exercise itself only through an exaggeration of the glycogen synthesis.

Bernhard, C. Melvin; and Bizot, William H. (*Louisville, Ky.*): SURGERY OF THE PATIENT WITH DIABETES MELLITUS. J. Kentucky M. A. 50:433-35, October 1952.

A resume of the surgical aspects of the patient with diabetes mellitus has been presented. Emphasis has been placed upon the fact that patients with this disease should enjoy the benefits of all surgery as long as their diabetes mellitus is under control. A plea is made for conservation of extremity amputation.

Bertino, Joseph; Dawson, Nancy; French, Rosalie; Margen, Sheldon; and Kinsell, Laurance W. (*Dept. of Med. and Inst. for Metabolic Res., Highland Alameda County Hosp., Oakland, Calif.*): COMPARATIVE OBSERVATIONS REGARDING UTILIZATION AND EXCRETION OF INFUSED GLUCOSE, FRUCTOSE AND INVERT SUGAR, RESPECTIVELY. J. Clin. Endocrinol. and Metab. *13*:658-61, June 1953.

Invert sugar and fructose when infused intravenously in nondiabetic subjects are utilized at a significantly more rapid rate than is glucose. As a corollary, there is less glycosuria.

Birdsong, McLemore; and Wood, James B. (*Charlottesville, Va.*): GALACTOSEMIA. Virginia M. Month. *80*:327-29, June 1953.

A brief discussion of chronic galactosemia is presented, stressing the importance of early diagnosis. Signs, symptoms and laboratory findings of the disease are outlined. A clinical case with a post-mortem report is presented.

Bishop, C. T. (*Div. of Applied Bio., Nat. Res. Laboratories, Ottawa, Canada*): DEGRADATION OF GLUCOSE. Science *117*:715-17, June 26, 1953.

The author reports a chemical method for glucose degradation in which all compounds formed are well-characterized crystalline compounds.

Bornstein, J. (*Dept. of Chem. Pathol., King's Coll. Hosp., London*): PLASMA INSULIN IN DIABETES MELLITUS. J. Endocrinol. 7: (Proc. Soc., LIX) October 1951.

It has been shown (Bornstein and Trewhella, 1950) that two types of diabetes exist—one type without and the other with detectable insulin in the blood. In the first type the diabetes may be due to a failure to secrete insulin, utilization in excess of the maximal secreting rate of the pancreas, destruction at a pathological rate, or an excess of substances tending to raise the blood sugar. However, whatever the cause, it can be stated that there is a lack of functioning insulin. In the second type it would appear that there is some interference with the normal function of insulin, although normal concentrations may be present in the plasma. It is also considered that if cases with a longer history were studied, intermediate forms would be found.

Boulin, R.; Chiménes, H.; and Tourneur, R. (*Paris*): A STUDY OF 14 CASES OF INSULIN LIPODYSTROPHY. La presse médicale 60:1024-27, July 1952.

Insulinic lipodystrophy is encountered in 2 to 6 per cent of cases of diabetes treated with insulin. Over nine tenths per cent of the cases observed were in women. The authors, who treated 14 cases of insulin lipodystrophy, state that they have obtained an excellent balance of the diabetes with doses of insulin far lower than those previously used, proceeding in such a way that an area of 1 square cm. should not receive more than one insulin injection per month and that 40 to 100 mg. of male hormone should be given by injection each week.

Burns, Thomas W.: Engel, Frank L.; Viau, Alberto; Scott, James L., Jr.; Hollingsworth, Dorothy R.; and Werk, Emile: (*Duke Univ. Durham, N. C.*): STUDIES ON THE INTERDEPENDENT EFFECTS OF STRESS AND THE ADRENAL CORTEX ON CARBOHYDRATE METABOLISM IN MAN. J. Clin. Invest. 32:781-91, August 1953.

A series of 280 glucose, insulin and glucose-insulin tolerance tests were performed on 150 normal subject and 53 ill patients in order to compare the effects of cortisone on carbohydrate metabolism in the presence and absence of the stress of illness.

In normal subjects, a single oral dose of 200 or 400 mg. of cortisone acetate was followed by a significant elevation of the blood sugar four hours later and impairment of the glucose tolerance test. No significant changes following the same treatment could be detected in the glucose-insulin or insulin tolerance tests with doses of insulin, ranging from 1/60 to 1/10 of a unit per kilogram intravenously. With 1/80 of a unit of insulin per kilogram, the total fall in blood sugar was not modified by cortisone treatment, but the level to which it fell was slightly higher than in the untreated group, indicating slight insulin insensitivity.

Chronic treatment of normal subjects with 200 mg. of cortisone daily for eight days did not modify the response to 1/60 of a unit of insulin per kilogram intravenously, but did abolish the blood sugar fall previously seen when glucose was administered simultaneously with 1/10 unit of insulin per kilogram intravenously. Ill subjects exhibited impaired glucose and glucose-insulin tolerance tests but normal insulin tolerance at all dose levels of insulin tested. The shapes of the curves of the impaired glucose and glucose-insulin tolerance tests in the ill subjects were significantly different from those of the normal individuals receiving cortisone.

Ill subjects pretreated for four hours with 200 mg. of cortisone-acetate showed significantly greater impairment of glucose tolerance and greater resistance to insulin than did normal subjects acutely or chronically treated with cortisone. Cortisone treated patients exhibited only slightly greater insulin resistance in the glucose-insulin tolerance test than did untreated patients, but markedly greater resistance than did normal subjects receiving cortisone acutely or chronically.

These observations are considered to be compatible with the concept that there is an interaction between stress and adrenal hormone in modifying carbohydrate metabolism. They are not reconcilable with the view that the metabolic alterations during stress are direct consequences of adrenal cortical hypersecretion.

Caso, Elizabeth K. (*Division of Chronic Disease and Tuberculosis, U. S. Public Health Serv., Boston*): USE OF DIABETIC DIET EXCHANGE LISTS. J. Am. Dietet. A. 29:687, July 1953.

During a 24-month period ending December 1952, a survey was made to determine how much the medical profession was using the booklet entitled *Meal Planning*

and Exchange Lists, recommended by a joint committee of the American Diabetes Association, the American Dietetic Association and the Diabetes Section, U.S. Public Health Service, which was published in 1949.

It was found that the booklet was used by hospitals and physicians in forty-eight states, Hawaii, Puerto Rico and the District of Columbia. At least 900 hospitals have adopted this method of diabetic meal planning, and it was estimated that probably 2,500 physicians were using this method in their practice.

Cavallero, Cesare; and Malandra, Bruno (*Instituto di Anatomia Patologica dell'Università de Milano, Italy*): HYPERGLYCEMIC AND GLYCOSURIC EFFECT OF GLUCAGON IN THE INTACT FORCE-FED RAT. Acta endocrinologica *13*:79-88, May 1953.

Adult intact male rats, force-fed on a high-carbohydrate, liquid diet and given cortisone, ACTH, STH, or glucagon, showed an increase of the urine and blood sugar. This effect was the most evident in cortisone and glucagon-treated groups. When glucagon was administered simultaneously with cortisone, ACTH or STH to the force-fed rat, it showed a high enhancing effect on glycosuria and glycemia. The combined treatment with glucagon and cortisone was the most effective in provoking a temporary diabetic condition. It is concluded that glucagon may be an important diabetogenic factor under favorable conditions.

Cheng, Tsung O.; Jaharaus, Robert C.; and Traut, Eugene F. (*Oak Park, Ill.*): EXTREME HYPERGLYCEMIA AND SEVERE KETOSIS WITH SPONTANEOUS REMISSION OF DIABETES MELLITUS. J.A.M.A. 152:1531-33, August 15, 1953.

From time to time extreme hyperglycemia has been recorded in the case of a patient who had an unusually high blood sugar but, after surviving profound and prolonged coma, apparently recovered completely from all symptoms and signs of diabetes mellitus. The patient's insulin requirement fell until finally she required none. The results of a glucose tolerance test three months after the acidosis were normal. She had been free from dietary restrictions for five months and enjoyed pastries, ice cream and other carbohydrate-rich foods, with no resulting glycosuria or hyperglycemia. She appeared to be in good health. A possible future relapse, however, cannot be excluded.

According to Zubrod, Eversole and Danna, a remarkable reduction in insulin requirement is found as Kimmelstiel-Wilson's syndrome progresses. Improvement has also been described as following limitation of diet and consequent loss of weight, cirrhosis, extirpation of pheochromocytoma, radiation of the pituitary gland in acromegaly, relief of Cushing's syndrome, control of hyperthyroidism, a large intake of sodium chloride, McCarey's experiment, myxedema and senescence. Temporary symptoms and signs of diabetes have also occurred after brain injury, pancreatic disease or hyperthyroidism. Maintenance of aglycosuria is often rewarded by a marked increase in the ability to tolerate much larger quantities of glucose-yielding food.

One of the authors also observed a 10-year-old boy with severe, persistent, classic, uncomplicated diabetes mellitus requiring 60 units of insulin for its control who, without apparent cause, lost all the symptoms and signs of diabetes mellitus during an observation of one year.

Constantinides, P. (*Anat. Dept., Univ. of British Columbia, Vancouver*): MAST CELLS AND SUSCEPTIBILITY TO EXPERIMENTAL ATHEROSCLEROSIS. Science *117*:505-06, May 8, 1953.

In a study of rats refractory to cholesterol-induced atherosclerosis and of rabbits highly atherosclerosis susceptible, the author observed in the connective tissues of the rat an extreme abundance of mast cells, which probably produce heparin, in contrast to an absence of such cells in the organs of the rabbit. The possibility that atherosclerotic or senile human subjects may present a mast-cell deficiency similar to that of rabbits is being investigated.

Cordes, Frederick C. (*Dept. of Ophthalmology, and the E. S. Heller Lab. of Eye Pathol., Univ. Calif. Med. Center, San Francisco, Calif.*): THE OCULAR CHANGES IN DIABETES AND THEIR EFFECT ON THE PATIENT'S VISION. Texas Rep. Biol. & Med. *11*:213-30, Summer 1953.

The conclusion of Dolger and others that there is vascular damage after 25 years of diabetes in virtually 100 per cent of cases is not shared by Joslin. He feels that the statistically high rate of damage is in part the result of poor treatment, and he cites 7 patients who have lived 25 years with diabetes and have shown no signs

of degenerative changes in the eyes or the vascular system elsewhere.

The author has seen a patient, a man of 48, who has had diabetes since he was 19 (29 years) and has controlled his disease carefully and constantly. He has normal vision in each eye, and his fundi show only a few scattered microaneurysms. Another patient, a woman of 60, has been a diabetic for 31 years (30 on insulin). With the exception of four instances, she has been under perfect control. The vision in each eye is 20/20. The fundi show in the right eye a few scattered aneurysms, a few superficial hemorrhages and some scattered, hard exudates. In the left eye, there are only a few exudates and a few microaneurysms.

Recently, Keiding and his co-workers reported their findings in a series of 451 patients with onset of diabetes under the age of 30 years and with duration of the disease for from 10 to 36 years. Among 32 patients who had maintained excellent or good control for 20 or more years, none had grade 5 (Wagener) retinopathy and only one had had grade 4 (Wagener) changes. On the other hand, in 157 patients with only fair or poor control, 16 per cent had grade 5 retinopathy and an additional 15 per cent had grade 4. No patient with excellent control had more than minimal retinopathy. It was found that in all stages of duration of diabetes the incidence of retinopathy and other complications was significantly less in patients who had maintained excellent or good control. Keiding and his group concluded that only by careful and constant control may the late complication of diabetes be prevented or postponed.

Thus, while almost all reports agree that the treatment of diabetes has no effect on the development of the retinopathy, recent scattered reports indicate that the prognosis may not be as black as is now believed, providing the present day methods of treatment are carried out meticulously. The physician, then, who accepts the diabetic as a patient has a grave responsibility in seeing to it that the patient has all the advantages of modern diabetes therapy. This trust is not to be taken lightly as it may mean, among other things, the preservation of the patient's vision.

Danowski, T. S. (*Univ. of Pittsburgh, Pittsburgh, Pa.*): STUDIES IN DIABETIC COMA AND ACIDOSIS: INTERRELATIONSHIPS OF URINARY POTASSIUM, SODIUM AND CHLORIDE. The Journal Lancet 73:224-26, June 1953.

More attention should be paid to the final composition of urine in diabetic coma as a determinant of the fate of administered electrolytes. It appears that a high excretion rate of any one constituent will tend to increase the excretion rates of others. If, for example, the intake of potassium is inadequate during a period of high sodium chloride output, this relationship could be expected to produce or further aggravate deficits of potassium. These grouped data afford no clue as to whether the interrelationship involves renal, extrarenal processes or both. The above data indicate that at lower rates of output the solutes of urine do not have as obligate a relationship to one another. Under such circumstances, the usual reliance upon the ability of the kidney to make adjustments in the excretion of individual electrolytes in accordance with deficiencies or excesses appears somewhat more justifiable.

De Duve, Chr. (*Univ. of Louvain, Belgium*): GLUCAGON: THE HYPERGLYCEMIC GLYCOGENOLYTIC FACTOR OF THE PANCREAS. Lancet 2:99-104, July 18, 1953.

According to Ferner (1951), metabolic equilibrium depends on a balance between the two opposed pancreatic secretions, insulin and glucagon; any large increase of one over the other leads to either spontaneous hypoglycemia or diabetes. It is certain that one may remove a large part of the pancreas or increase the amount of active pancreatic tissue by grafting without creating observable metabolic disturbances; whereas the appearance of an islet adenoma predominantly containing beta-cells causes spontaneous hypoglycemia, and the destruction of the beta-cells leads to diabetes. The diabetic state which follows the total removal of the pancreas and its alleviation by hypophysectomy can still be partly explained on the basis of this concept, since active alpha-cells are left in the gastric mucosa of the depancreatized dog and may be stimulated there by growth hormone. However, the various metabolic effects of growth hormone, of the adrenocortical hormones, and of the thyroid are not sufficiently taken into account in this picture, which also fails to emphasize the fact that a minimum absolute amount of insulin is essential for normal metabolism. The facts remain that glucagon has become an important factor in all considerations of the etiology of diabetes and that many of our concepts on the interrelationships between the endocrine glands will have to be revised in the light of the new knowledge which has accumulated. There is now a reasonable body of coherent and mutually confirming data indicating that glucagon is the long-sought hormone of the alpha-cells of the pancreatic

islets and that it is involved in the physiological regulation of metabolism and, presumably, of growth.

Dejean, Ferdinand A. (*Baton Rouge, La.*): DIABETIC COMA. New Orleans M. & S. J. *104*:656-60, October 1952.

There are several important factors in the treatment of diabetic coma: (1) early recognition; (2) early administration of insulin in large doses; (3) early correction of chemical changes in the blood by means of sufficient fluids and alkalis; (4) a careful watch for hypopotassemia and hypoglycemia; (5) return of patient to oral medication as soon as possible; and (6) careful search for the condition that precipitated the coma.

Dolger, Henry (*Diabetic Clin., Mt. Sinai Hosp., New York, N. Y.*): MANAGEMENT OF DIABETES MELLITUS. M. Clin. North America 715-31, May 1953.

The author outlines his objectives of treatment which are an adequate diet for normal activity, sufficient insulin to assure adequate utilization of the diet and simplification of the regimen so as not to interfere with the usual work and living habits of the patient.

Discussion of the treatment of diabetes without insulin is presented as follows: (1) In the obese patient low-caloric diet may be sufficient. (2) In the patient with asymptomatic, transient or casual glycosuria or in a patient with hyperglycemia without glycosuria, simple omission of sugar, pastry and soft drinks can be used. (3) Carbohydrate restriction alone should be used in a therapeutic trial in the average adult of normal weight, mild to moderate glycosuria, with or without symptoms. If glycosuria persists without symptoms, further carbohydrate reduction is warranted. Alcohol is permitted. The author's criteria for management are: (1) Fasting blood sugar of not more than 200 mg. per cent. (2) Disappearance of glycosuria. (3) Maintenance of normal weight and vigor. (4) Subnormal weight is contraindication to dietetic treatment alone. The education of a diabetic not requiring insulin is discussed.

The indications for immediate insulin therapy are: (a) ketosis, (b) classical symptoms without ketonuria, (c) complications as infection, hyperthyroidism and preparation for surgery, when accompanied by glycosuria. Insulin is also indicated after a trial of dietary restriction if there is failure to check persistent glycosuria, or loss of weight and strength. The author discusses the limitations in insulin therapy and the types of insulin available for use and their indications and duration of action.

Three general rules in dietary-plus-insulin management are presented. (1) Obesity requires weight reduction by caloric restriction. (2) The aged may be maintained slightly overweight. (3) The remaining patients should be treated according to normal nutritional standards. A discussion of the use of *a normal diet* is presented.

The author feels that if glucose excretion does not exceed 15 per cent of the total carbohydrate intake, the patient can maintain weight and strength, be free from acetonuria and azoturia, improve carbohydrate tolerance, have normal wound healing, and antibody production, and insure normal growth and development in children. In elderly patients with arteriosclerosis or heart disease, one should guard against hypoglycemia. In patients who require large amounts of insulin or who are "brittle" or juveniles, clinical control should be relied upon instead of the degree of glycosuria.

Duncan, Garfield G. (*Philadelphia, Pa.*): DIABETIC COMA—PATHOLOGIC PHYSIOLOGY AND TREATMENT. Connecticut M. J. *17*:493-97, June 1953.

Disregard of the degrees of hyperglycemia and glycosuria increases the likelihood of and decreases the natural resources used to combat diabetic coma. Hence, poor control of diabetes plus conditions which rapidly intensify the need for insulin are the precipitating causes of diabetic coma. Most fatalities are from circulatory failure—showing the importance of the disturbances in fluid and mineral balances.

A test for ketones in the blood is recommended. Two drops of plasma can be used with the ordinary reagents. There is always a 4-plus reaction if the patient is in diabetic coma.

In starting treatment it is quite safe to give 100 units of regular insulin as an initial dose (including 40 units intravenously), followed by 50 units every half hour. The decreasing need for insulin is shown by decreasing ketonemia. A test for plasma acetone every 2 hours is advised until ketonemia has been reduced to an insignificant degree.

There is accumulating evidence that fructose, administered in the presence of ketosis, is more rapidly utilized than is glucose. It is probable that the intravenous administration of fructose with the initial saline solution will become part of our therapy for diabetic

coma. Because of the rapid removal of fructose from the blood and its prompt utilization, it may provide the benefits we have desired of glucose without its reputed untoward influences.

The author gives potassium chloride orally, 1 gm. every 2 hours for five to eight doses, beginning after six hours of therapy, providing renal function is good. Potassium chloride may be given intravenously in a 1.14 per cent solution if its administration orally is impracticable. The author gives sodium lactate solution in an amount calculated to raise the CO_2 combining power 10 to 15 volumes per cent.

Duncan, Garfield G. (*Philadelphia, Pa.*): OBESITY AND DIABETES. Pennsylvania M.J. 56:821-23, September 1953.

The obese diabetic patient not receiving insulin has a mild case of diabetes irrespective of the degree of glycosuria or hyperglycemia. Proof of this claim is readily provided. The glycosuria and hyperglycemia disappear, and (as proved by Allen in 1914) the diabetes is forced into the background merely by restricting the total caloric intake sufficiently to bring about a reduction in body weight. The glucose tolerance test may give normal values if the reduction in weight is great. But, this favorable trend is reversed and the subjective and objective evidences of diabetes return with the resumption of the obese state. The obese diabetic is especially prone to have atherosclerosis, essential hypertension, cutaneous disorders and cholelithiasis. The atherosclerotic processes affect particularly the coronary arteries and the arteries of the extremities. The frequency and dangers of coronary insufficiency—angina pectoris and occlusion of the coronary arteries—and of obliterative vascular disease of the extremities are prevalent in obese diabetic patients.

Eberlein, Walter R. (*Baltimore, Md.*): AMINOACIDURIA IN CHILDHOOD: CYSTINURIA AND CYSTINOSIS. Am. J. M. Sc. 225:677-86, June 1953.

The author reviews the nature and extent of aminoaciduria in normal individuals and in two abnormal states—cystinuria and cystinosis (de Toni-Fanconi syndrome)—in the light of recent studies based largely on the use of paper chromatography and microbiologic assays.

The urinary amino-acid excretion pattern, especially with the ten essential amino acids, normally remains reasonably constant from day to day. Excessive aminoaciduria in conjunction with hyperaminoacidemia occurs with (a) liver disease, especially acute yellow atrophy, (b) administration of cortisone or corticotropin, and (c) phenylpyruvic oligophrenia with its hepatic enzymatic disturbance in the conversion of phenylalanine to tryosine. Excessive aminoaciduria without hyperaminoacidemia occurs in consequence of renal tubular dysfunction in (a) nephrosis, (b) hepatolenticular degeneration, (c) cystinuria and (d) cystinosis.

In cystinuria, the normal pattern of urinary sulfur excretion is disturbed, with a reduction in the inorganic sulfate portion from 90 to 40 per cent and an increase in the cystine portion from 5 to 55 per cent. Not only is cystine excreted in excess but also lysine and arginine. The defect is probably in the tubular reabsorption of all diamino acids, with cystine which is the least soluble in an acid medium precipitating out in the urinary tract and thereby predisposing to the formation of calculi and secondary renal tract damage. Prophylactically helpful should be an alkaline ash diet and alkaline salts.

Cystinosis is less clearly understood, but the clinical syndrome developing in infancy with polyuria, often glycosuria, failure of growth, development of rickets, renal failure and "crises" of fever, dehydration, acidosis and hypokalemia, appears to result from an excessive excretion of at least 10 amino acids, deposition of cystine crystals in liver, spleen, lymph nodes and bone marrow, and renal damage with secondary rickets. There is evidence to suggest a defect in the proximal renal tubular phosphatases involved in the reabsorption of glucose, phosphorus and amino acids. The old view that all cases died in infancy has been superseded by the demonstration of adult cases dying with liver disease. Preliminary reports indicate good therapeutic results in cases treated with Shohl's citric acid-sodium citrate solution, potassium chloride and high doses of vitamin D, with subsidence of the aminoaciduria and healing of the rickets.

Editorial (*London, England*): COMPLICATIONS OF DIABETES. British Medical Journal 1:1438-39, June 27, 1953.

The complications of diabetes may affect any system of the body, and relatively few diabetics escape them completely. Some practical points emerge from consideration of the complications of diabetes. The importance of routine urine testing, whatever a patient's presenting complaint, should hardly need stressing; but even in

the absence of glycosuria a blood sugar curve may occasionally be helpful in diagnosis. Secondly, full clinical examination of all diabetics at regular intervals is clearly essential. Not only will this often lead to the finding of lesions in the nervous system, the vascular system, the eyes and the kidneys, but now and then it will also bring to light an associated disease such as hemochromatosis. This condition is probably not so rare as was formerly thought; its recognition has been simplified by the discovery of characteristic serum iron changes, and its early diagnosis assumes more importance in view of the possibility of treatment by phlebotomy.

Editorial (*London, England*): PROGNOSIS IN DIABETIC PREGNANCY. British Medical Journal *1*:1440, June 27, 1953.

A discussion of the outlook for the pregnant diabetic and her baby is based on observation of Dr. Wilfred Oakley. Although the outlook for the pregnant diabetic in terms of mortality and morbidity continues to improve, the prognosis for the baby remains clouded by a fetal loss of over 25 per cent, a high rate which Oakley finds largely unexplained. He is unable to support views that the fetal loss is related to the duration or severity of the diabetes or to the age of its onset. In particular, his figures deny that toxemia is the cause of high fetal death rate, and he therefore concludes that any form of therapy directed against toxemia cannot appreciably increase the fetal salvage rate. This conclusion is diametrically opposed to the views of Dr. Priscilla White in Boston, as expressed most recently in a full account of 525 viable pregnancies in diabetic women treated between 1936 and 1951.

Eskind, Irwin B.; Franklin, William; and Lowell, Francis C. (*Boston, Mass.*): INSULIN-RESISTANT DIABETES MELLITUS ASSOCIATED WITH HEMOCHROMATOSIS. Ann. Int. Med. *38*:1295-1306, June 1953.

The clinical course of a patient with a high degree of resistance to insulin is described. Death apparently occurred directly or indirectly from a severe hypoglycemic reaction to insulin at a time when the patient's resistance was decreasing. Hemochromatosis, discovered at autopsy, did not appear to play a part in the patient's course. A series of insulin tolerance tests indicated that resistance to human insulin was less marked than that to commercial insulin. The patient's blood contained an insulin antagonist, presumably an antibody, demonstrable in mice. The patient was sensitive by skin test to both commercial and human insulins and the blood containing skin-sensitizing antibody for both.

Evarts, Edward V.; Browne-Mayers, Albert N.; and Rosenbaum, Leanore (*New York, N.Y.*): THE EFFECT OF ATROPINE ON THE ELECTROENCEPHALOGRAM DURING INDUCED HYPOGLYCEMIA. Third International Congress of Electroencephalog. & Clin. Neurophysiol., P. 31-32, August 17-22, 1953.

Six psychiatric patients undergoing insulin treatments were given 1.2 mg. of atropine intravenously in 2 minutes. Electroencephalographic changes were quantitated by analysing monopolar left occipital potentials using an Offner frequency analyser; analyser deflections were measured and plots made of relative energy in frequency bands 3 through 12 cps. Blood sugar determinations were made 5 minutes before, at the time of, and 5 minutes after administration of atropine. The results fail to show an effect of atropine on the electroencephalogram during hypoglycemia.

Faloon, William W. (*State Univ. of New York Med. Coll., Syracuse, N. Y.*): NITROGEN METABOLISM AND FOOD INTAKE IN NONTUBERCULOUS PATIENTS RECEIVING ISONIAZID. Am. Rev. Tuberc. *68*:207-11, August 1953.

This study was made on 3 nontuberculous patients because of the noted marked increase in appetite and body weight when tuberculous patients were treated with isoniazid. It was speculated that the drug might have an anabolic effect independent of its action on the tuberculous infection.

Cases studied were convalescing pneumonia, chronic hepatitis and nontropical sprue. Nitrogen contents of diet, urine and stools made by macro Kjeldahl method for periods of 18 days did not demonstrate any signicant evidence of a specific anabolic effect of isoniazid.

Ford, Malcolm J. (*Jacksonville, Fla.*): THE INTEREST OF PUBLIC HEALTH IN DIABETES. Pub. Health Rep. *68*:624-27, June 1953.

In the control of diabetes mellitus, the author considers the public health agency both a catalyst and an auxiliary

force—a catalyst which speeds up the discovery of all cases of diabetes through community action and an auxiliary force which assists the practicing physician in giving the diabetic patient the detailed information which he needs to control his disease and live with it successfully.

Foreign Letters (*Australia*): RECORD INCIDENCE OF DIABETES. J.A.M.A. *152*:624, June 13, 1953.

Sydney has one of the highest diabetes rates in the world, stated Dr. R. D. Lawrence, physician and world authority on diabetes, to the King's College Hospital in London. Two per cent of Sydney's population have diabetes, compared with one-half of one per cent in England and one and one-half per cent in the United States. Doctor Lawrence ascribed this high incidence to overeating.

French, Geoffrey (*Kolar Gold Field, India*): POLYARTERITIS NODOSA PRESENTING AS ACUTE DIABETES MELLITUS: CASE REPORT. British Medical Journal *1*: 1262, June 6, 1953.

In this case, the only known possible antigens were the *Bacterium typhosum* and aspirin, but the former rests only on the evidence of a positive Widal reaction, which may have been an anamnestic reaction in the absence of positive blood, stool or urine cultures. It is believed that the acute diabetes was due to an associated acute hemorrhagic pancreatitis.

Garland, Hugh; and Taverner, Dereyck (*Univ. of Leeds, England*): DIABETIC MYELOPATHY. British Medical Journal *1*:1405-08, June 27, 1953.

Attention is drawn to a form of diabetic neuropathy previously described 60 years ago but forgotten. The syndrome consists of asymmetrical pain, weakness, muscle wasting and areflexia in the legs, without objective sensory disturbance, in middle-aged patients with diabetes mellitus of relatively short duration. The protein content of the cerebrospinal fluid is usually raised. The plantar responses are often extensor, and the electromyographic changes in the affected muscles are compatible with a myelopathic lesion. Five new examples of the syndrome are described and the literature is reviewed.

Goldstein, M. S.; Henry, W. Lester; Huddlestun, B.; and Levine, Rachmiel (*Dept. of Metabolic and Endocrine Res., Med. Res. Inst., Michael Reese Hosp., Chicago, Ill.*): ACTION OF INSULIN ON TRANSFER OF SUGARS ACROSS CELL BARRIERS: COMMON CHEMICAL CONFIGURATION OF SUBSTANCES RESPONSIVE TO ACTION OF THE HORMONE. Am. J. Physiol. *173*:207-11, May 1953.

Employing eviscerated, nephrectomized dogs, the authors studied the distribution volume of a series of pentoses and hexoses before and after insulin administration. Technical difficulties associated with the quantitive analysis of certain sugars in the presence of glucose were obviated either by administering the sugar after the blood glucose was dropped virtually to zero or by subjecting the blood to yeast fermentation for glucose removal prior to the determination of the nonfermentable sugar. It was observed that insulin increased the distribution volume only of sugars with a chemical configuration at carbons 1, 2 and 3, similar to that of d-glucose (d-galactose, l-arabinose and d-xylose), while sugars with a different configuration (d-arabinose, l-rhamnose, d-sorbitol, d-mannose, d-fructose, l-sorbose) were not so affected, regardless of whether or not the particular sugar was utilized. This work strengthens the postulate that the physiologic action of insulin is to facilitate the transfer of glucose, as a free hexose, from the extracellular fluid to the intracellular space in certain organs and tissues.

Goldstein, M. S.; Mullick, V.; Huddlestun, B.; and Levine, Rachmiel (*Dept. of Metabolic and Endocrine Res., Med. Res. Inst., Michael Reese Hosp., Chicago, Ill.*): ACTION OF MUSCULAR WORK ON TRANSFER OF SUGARS ACROSS CELL BARRIERS: COMPARISON WITH ACTION OF INSULIN. Am. J. Physiol. *173*:212-16, May 1953.

The authors investigated in eviscerated, nephrectomized dogs and rats the comparative status of other sugars in relation to the well-established fact that the muscular work even in diabetic animals increases the rate of uptake of glucose by the tissues. Under these experimental conditions, it was observed that muscular work promoted cellular entry of three sugars possessing the same chemical configuration as d-glucose at carbons 1, 2 and 3, despite the absence of utilization of these sugars (d-galactose, l-arabinose and d-xylose). This constitutes a phenomenon in the case of muscular work parallel to that proposed by this laboratory for the action of insulin, i.e., a primary action on facilitating transfer

across cell surface barriers of sugars with a certain chemical configuration. Since this effect is noted throughout the body in the case of a local and neurologically isolated vigorously working muscle group, it is postulated that a humoral product of contracting skeletal muscle can activate a transfer mechanism across cell surface barriers for certain types of sugars.

Goodman, Joseph I. (*Cleveland, Ohio*): CAUSES OF DISABILITY IN PATIENTS WITH CHRONIC DISEASE. J.A.M.A. *152*:1336-38, August 1, 1953.

In contrast to its high incidence in the general population, diabetes mellitus per se is not a disabling condition.

Gourevitch, A.; and Whitfield, A. G. W. (*Dept. Surg. and Med., Queen Elizabeth Hosp., Univ. of Birmingham, England*): TOTAL PANCREATECTOMY. British Journal of Surgery. *40*:104-111, 1952.

The author reports on a patient subjected to total pancreatectomy. The patient was discharged on a diet of carbohydrate, 200; fat, 75, and unlimited protein, with 15 units of regular insulin and 15 units of protamine zinc insulin together with 60 gr. of pancreatin 3 times daily. The low requirement of insulin postoperatively lends support to the current belief that there are important extrapancreatic factors in diabetes. The literature contains numerous references to the marked insulin sensitivity of depancreatized human beings, including a report of a patient who died from hypoglycemia following total pancreatectomy.

Graubarth, Harry; Mackler, Bruce; and Guest, George M. (*Children's Hosp., Res. Foundation and the Dept. of Pediat., Univ. of Cincinnati Coll. of Med., Cincinnati, Ohio*): EFFECTS OF ACIDOSIS ON UTILIZATION OF GLUCOSE IN ERYTHROCYTES AND LEUCOCYTES. Am. J. Physiol. *172*:301-08, February 1953.

A technic that permits separate estimation of glycolysis in red and white blood cells and in samples containing varying mixtures of the two types of cells in their own plasma was applied to studies of glycolysis in human and dog blood, at normal *p*H and after acidification in vitro, and in blood drawn from dogs in states of severe acidosis induced by prolonged intravenous infusions of ammonium chloride. In normal dog's blood, at 37°C. and with normal *p*H, glycolysis averaged 0.018 ug. of glucose disappearing per hour per million red cells and 9.9 ug. per hour per million white cells; thus, the rate for the white cells was 500 to 600 times faster than that of the red cells. Glycolysis was inhibited in acidotic blood, more in the erythrocytes than in the leucocytes. In four samples of dog blood with *p*H around 7.0, the rates of glycolysis for red and white cells respectively averaged 0.006 and 6.0 ug. per hour per million cells. Correction of the *p*H values to normal by the addition of sodium bicarbonate restored the rates of glycolysis to normal for both red and white cells.

Grinspoon, Lester; Sagild, Uffe; Blum, Harold P.; and Marble, Alexander (*Elliott P. Joslin Camp for Diabetic Boys, Charlton, Mass., and Baker Clin. Res. Lab., Boston, Mass.*): CHANGES IN CIRCULATING EOSINOPHILS IN JUVENILE DIABETICS IN RESPONSE TO EPINEPHRINE, ACTH AND HYPOGLYCEMIA. J. Clin. Endocrinol. & Metabolism *13*:753-68, July 1953.

The mean fall in circulating eosinophils following epinephrine in controlled juvenile diabetics was significantly less than that obtained in nondiabetics. In the diabetics, the epinephrine tests were made both in the forenoon when the blood sugar level was relatively high and in the afternoon when it was generally lowest. There was no significant difference in the responses obtained at these two times.

Observations of the eosinophil count and insulin dosage in a patient with diabetes and Addison's disease are reported. Insulin hypoglycemia induced an eosinophil response which could not be correlated with the blood sugar level and the response to the epinephrine test made under conditions of relative normoglycemia.

It is concluded that the low mean response to the epinephrine test and to the ACTH test in juvenile diabetics may be explained on the basis of adrenal cortical unresponsiveness, which has been assumed by some workers to be synonymous with adrenal cortical insufficiency. It is suggested that rapid changes in blood sugar concentration may constitute a stress, necessitating a high level of adrenal cortical function, which may ultimately lead to a state of relative adrenal insufficiency.

Guest, George M.; Mackler, Bruce; Graubarth, Harry; and Ammentorp, Peter A. (*Children's Hosp. Res. Foun-*

dation and the Dept. of Pediat., Univ. of Cincinnati, Coll. of Med., Cincinnati, Ohio): RATES OF UTILIZATION OF GLUCOSE IN ERYTHROCYTES AND LEUCOCYTES. Am. J. Physiol. *172*:295-300, February 1953.

For estimating rates of glycolysis by erythrocytes and leucocytes in mixtures of the two types of cells, heparinized whole blood was centrifuged and divided into two samples, one of red cells with few or no white cells and the other of red cells with many white cells, resuspended in their own plasma. Silicon-coated glassware was used throughout the procedure to minimize cellular damage. The samples were placed in flasks gassed with 5 per cent CO_2 to maintain the *p*H constant and shaken in a bath at 37 degrees C. Concentrations of sugar were determined at suitable intervals. Glycolysis was expressed in micrograms of sugar removed per hour per million cells, red and white, in each sample. Separate rates of glycolysis by red and white cells were calculated by solving simultaneous equations derived from the two sets of data.

In samples of blood from 3 normal dogs and 10 normal human subjects, rates of glycolysis varied from 0.014 to 0.028 ug. of glucose per hour per million erythocytes and from 4.7 to 13.2 ug. per hour per million leucocytes, indicating a rate of glycolysis 300 to 900 times faster in white cells than in red cells and establishing that both cell types play significant roles in the process. Glycolysis by blood platelets appeared to be insignificant. Blood glycolysis represents a small, but not inconsequential, part of the body's total use of carbohydrate, amounting to 15 or 20 gm. per day for an average adult with normal cell count and to much more probably in febrile diseases with leukocytosis and in leukemia.

Gupta, N. N. (*Lucknow, India*): REVERSIBLE DIABETIC SIXTH NERVE PALSY. British Medical Journal *1*:1390, June 20, 1953.

The sixth is the cranial nerve most easily paralyzed in intracranial disorders, especially in conditions of increased intracranial tension or basal meningitis. Diabetic neuritis has also been a recognized cause of a sixth nerve lesion, but, considering the wide incidence of diabetes mellitus, such involvement is a rarity. A man 50 years of age was admitted for diplopia of six weeks' standing. He had typical right-sided rectus paralysis. No other neurological lesion was elicited. There was no history of headache. He had had symptoms of polyuria, increased appetite, and thirt for about two years, but he had never sought medical advice. Treatment consisted of a diet of 300 gm. carbohydrate, 66 gm. fat and 76 gm. proteins, together with 30 units of insulin a day and 50 mg. vitamin B_1 once a day. This kept the patient sugar-free and within a period of four weeks cured his sixth nerve paralysis as well as the pain in his calf muscles. He remained symptom-free for the next four weeks of observation.

Guth, Paul; Komarov, S. A.; and Shay, Harry (*Samuel S. Fels Res. Inst., Temple Univ. Sch. of Med., Philadelphia, Pa.*): PHOTOTURBIDIMETRIC DETERMINATION OF PANCREATIC AMYLASE. Am. J. Physiol. *173*:461-66, June 1953.

By the phototurbidimetric method of Waldron and two modifications of it, rectilinear regression of percentage of digestion of the starch suspension on log of protein nitrogen was found over a wide range of enzyme concentrations. This offers a convenient and sufficiently accurate way of determining amylase content of pancreatic juice. The results also indicate a constancy of the ratio of amylase to protein nitrogen concentration.

Harvey, H. I.; and Simmons, W. D. (*Herrick Mem. Hosp., Berkeley, Calif.*): WEIGHT REDUCTION: A STUDY OF THE GROUP METHOD; PRELIMINARY REPORT. Am. J. M. Sc. *225*:623-25, June 1953.

The group approach to weight reduction appears effective in bringing about satisfactory weight loss for a majority of participants. In a program scheduled for 16 weeks for testing purposes, 93 of an original 109 participants attended four or more weekly meetings; 77 lost 10 or more pounds and only one lost no weight. No appreciable difference in weight loss occurred in groups placed under leaders who conducted a "nutritionally centered" and a "psychologically centered" approach. For homogeneity, groups were composed of approximately 14 members, each divided into below and above age 40. The group itself appears to satisfy whatever need may exist for psychotherapy in most overweight individuals. Long-term follow-up is believed necessary to demonstrate whether there will be significant achievement and maintenance of ideal weight goals, in order to determine the ultimate effectiveness of group methods for community projects.

Henry, Richard J.; and Berkman, Sam (*Beverly Hills, Calif.*): CORRESPONDENCE: ERRORS IN LABORATORY PROCEDURES. J.A.M.A. *152*:1166-67, July 18, 1953.

Surveys of laboratory accuracy have given adequate proof that too many laboratory reports are in such gross error and that they are not only misleading but, at times, a cause of serious errors. Yet, assuming every laboratory procedure was perfectly performed, there would still be error through no fault of the laboratory and beyond reasonable control.

As an example of the variation of results obtained when a test is repeated on the same sample, a figure is presented showing the distribution of the results of 30 analyses for blood sugar on a pooled blood sample run by the Folin-Wu method. A report of a blood glucose level of 106 mg. per 100 cc. does not mean that the exact level is actually 106; in fact, the probability is that it is not 106. What it does mean is that the correct answer for the method used is probably (95 per cent confidence) within 10 mg. of the reported figure. The same situation exists in all clinical chemical analyses. Ideally, all reports should be given with an indication of the error associated with them.

There are a number of factors that contribute to this unavoidable error. Every step in a chemical procedure cannot be reproduced exactly and contributes its share of error to the total, over-all error of the tests.

In the field of hematology, the unavoidable errors are not sufficiently appreciated. A physician receives a report on an erythrocyte count of 3,800,000, places the patient on iron therapy, repeats the count a week later, and receives a report of 3,400,000. At this point, the laboratory is apt to be blamed for poor work. Actually, the laboratory may well be correct in both counts. The true count, in the instance in which 3,800,000 erythrocytes are reported, is probably between 3,100,000 and 4,500,000.

Nearly every procedure performed in the clinical laboratory could be discussed from the standpoint of unavoidable or permissible error.

Hirson, Cedric; Feinmann, E. L.; and Wade, Henry J. (*Salford Royal Hosp., England*): DIABETIC NEUROPATHY. British Medical Journal *1*:1408-12, June 27, 1953.

About half of all cases of diabetes mellitus show evidence of neurological disease. Diabetic neuropathy may be divided into three groups: (a) hyperglycemic—related to failure of diabetic control and rapidly relieved by routine treatment; (b) active—the most serious form, present in about 3 per cent of all cases, apparently unrelated to diabetic status and with a tendency to remission and relapse; and (c) asymptomatic—chronic, permanent and not disabling. There is no good evidence that arteriosclerosis or vitamin B deficiency are causal agents. The neuropathic process seems to be inherent in some cases of diabetes. The production of gangrene, neurogenic bladder and joint change by diabetic neuropathy is of practical importance.

Hollander, Lester; and Zinn, Lynwood D. (*Pittsburgh, Pa., and Clarksburg, W. Va.*): FAILURE OF DENATURED INSULIN IN THE PREVENTION OF URTICARIA CAUSED BY INSULIN. A.M.A. Arch. Dermat. & Syph. *67*:513-14 May, 1953.

The authors cite a case of insulin allergy in which the use of denatured insulin was tried unsuccessfully. The denatured insulin was prepared, as originally suggested by Dolger, by immersion of the vial of insulin in boiling water for thirty minutes.

Hollis, Ben H.; and Hurst, Arthur T. (*Louisville, Ky.*): DIAGNOSIS OF DIABETES MELLITUS. J. Kentucky M. A., *50*:427-29, October 1952.

The death rate in the state of Kentucky from diabetes has been given with the median age at death. It is observed that the median age has increased 7.9 years since 1915. Diabetes rates eleventh as a cause of death. The symptoms of diabetes are discussed with the observation that they are more often absent than present in this era. Potential diabetics should have periodic examinations. It is recommended that the postprandial blood sugar examination be made a part of the routine laboratory examination. The value of diabetes detection drives is recognized, and it is recommended that all physicians assist in this work.

Honjo, Ichio; and Araki, Chisato: (*Kyoto Univ. Med. School Hosp., Kyoto, Japan*): TOTAL PANCREATECTOMY. J. Internat. Coll. Surgeons *19*:692-703, June 1953.

The development of the fatty liver after total pancreatoduodenectomy, which has been observed in dogs and is supposed to be the greatest obstacle in carrying out this

operation, does not seem to be an unavoidable sequel in man. In addition, the authors have obtained some results contributing to the knowledge about susceptibility to insulin after total pancreatoduodenectomy and about the physiologic significance of serum diastase. By these results the authors are firmly convinced that, if the indications are properly discerned, this kind of operation may be performed on man without much postoperative danger.

Houssay, B. A.; and Rodriguez, R. R. (*Inst. of Biol. and Experimental Med., Costa Rica, Buenos Aires, Argentina*): DIABETOGENIC ACTION OF DIFFERENT PREPARATIONS OF GROWTH HORMONE. Endocrinology 53:114-16, July 1953.

Dogs became very sensitive to the diabetogenic action of three growth hormone preparations following subtotal pancreatectomy (77-87 per cent of the pancreatic mass resected). Two preparations obtained by the Raben method also showed a definite diabetogenic action. The Armour preparation of growth hormone obtained by the Wilhelmi-Fishman-Russell method had more growth-promoting and more diabetogenic activity than the Armour preparation of growth hormone obtained by the Raben method. The diabetogenic action of the growth hormone preparations was observed in the absence of the thyroid gland.

Ingle, Dwight J.; Beary, Dexter F.; and Purmalis, Andrejs (*Res. Lab., The Upjohn Co., Kalamazoo, Mich.*): RELATIONSHIP OF THE ADRENAL GLANDS TO THE DIABETOGENIC EFFECT OF ETHYLENDIAMINE IN THE PARTIALLY DEPANCREATIZED RAT. Endocrinology 53:30-36, July 1953.

These studies were designed to test the hypothesis that ethylenediamine causes exacerbation of diabetes in the partially depancreatized rat via activation of the anterior pituitary-adrenal cortex axis. Partially depancreatized male rats were force-fed a medium carbohydrate diet by stomach tube. Ethylenediamine was injected in amounts of 0.05 ml. once daily for 5 days and twice daily for 5 days in each of 4 experiments. In Experiment 1, ethylenediamine was found to cause a rise in the level of blood glucose as well as in urinary glucose. In Experiment 2, ethylenediamine caused exacerbation of the diabetes of adrenal demedullated rats. In Experiment 3, moderately diabetic adrenalectomized rats treated with 3 glycogen units daily of ACE (adrenal cortical extract) failed to show exacerbation of the diabetes during the injection of ethylenediamine. It was postulated that ethylenediamine (a noxious agent) may have an extra-adrenal diabetogenic action which is masked by the development of adrenal cortical insufficiency in rats on a fixed intake of ACE adequate to meet the needs of non-stressful conditions only. Experiment 4 was a partial test of this hypothesis. Very mildly diabetic adrenalectomized rats were treated with 5 glycogen units of ACE per day. The injection of ethylenediamine caused exacerbation of the diabetes in each of the adrenalectomized rats, but the response was greater in nonadrenalectomized animals. These experiments show that ethylenediamine has an extra-adrenal effect upon glycosuria, but that the response is modified by removal of the adrenal glands.

Kinsell, Laurance W. (*Highland Alameda County Hosp., Oakland, Calif.*): RELATIONSHIP OF POTASSIUM TO "STEROID DIABETES" IN GENERAL AND STEROID HORMONE-INDUCED INSULIN RESISTANCE IN PARTICULAR. Lancet 73:222-24, June 1953.

Adrenocorticotropic hormone, compound E and compound F have been administered to diabetic patients as part of a study designed to evaluate the effect of cortical steroids upon certain aspects of lipid metabolism. In evaluating the metabolic data in patients treated in this manner, it was noted that a major loss of base occurred during the period of development of insulin resistance and that potassium loss was relatively greater than in the case of any other single basic ion measured. Since potassium ion was known to be associated with certain aspects of carbohydrate metabolism, it was postulated that the potassium loss per se was responsible in whole or in part for the development of insulin resistance during the administration of ACTH and cortisone. Accordingly, in the organization of further studies in diabetics, potassium was administered in relatively large amounts during the time of administration of ACTH and cortisone. Under these circumstances, no insulin resistance developed. The administration of sodium instead of potassium to patients under these conditions has so far failed to produce a comparable effect. It would therefore appear that the depletion of potassium ion is an essential part of the total "diabetogenic" effect of cortical steroids. The precise mechanism of this effect is by no means clear, but the following possibilities must be considered: Potassium prevents resistance to insulin, and/or increases sensitivity to insulin, and/or increases production of endogenous insulin.

Knight, William A. Jr.; and Muether, R. O. (*Dept. of Internal Med., St. Louis Univ. Sch. of Med., St. Louis, Mo.*): CARCINOMA OF THE PANCREAS: THE COMPARISON OF CLINICAL AND LABORATORY FINDINGS OF CARCINOMA OF THE PANCREAS AND CHRONIC PANCREATITIS. South. M. J. *46*:660-67, July 1953.

On the basis of 88 cases of carcinoma of the pancreas confirmed by biopsy or autopsy and of 58 cases of chronic pancreatitis diagnosed by elevated serum diastase levels and an associated compatible clinical history, the authors discuss the differential diagnosis of these diseases in terms of clinical and laboratory findings.

Carcinoma of the pancreas occurred three times more frequently in males, with increasing incidence with age from the fourth through the eighth decades. It was a disease of rapid progression and relatively short duration, which ranged from 0.5 to 32 months with an average of 7.5 months. By contrast, chronic pancreatitis occurred equally in both sexes, developed fairly uniformly from the third through the eighth decades, with a maximum incidence by the sixth, and its duration extended over many years.

The symptoms of the two states were so similar as to preclude differentiation on this basis, but the most frequent symptoms in carcinoma were pain, weakness, jaundice, weight loss and anorexia. In pancreatitis they were pain, weight loss, malaise and gastro-intestinal symptoms. All patients with pancreatitis exhibited pain and weight loss during the course of their illness while 26 per cent of the patients with cancer had only one of these symptoms.

While the physical findings in chronic pancreatitis may be indefinite and jaundice may be transitory, carcinoma may exhibit outstanding findings such as ascites, a palpable gall bladder or a palpable mass and persistent jaundice.

No single laboratory test or battery of tests established the differential diagnosis, but three procedures appeared to be of some value; (1) repeated serum amylase determinations, (2) glucose tolerance tests and (3) serum alkaline phosphatase determinations. While a single serum diastase analysis was of no value, when performed serially the amylase values in carcinoma exhibited a progressive fall from initially elevated to consistently minimal levels, in sharp contrast to pancreatitis which showed considerable fluctuation in repeated tests. The glucose tolerance test was abnormal in 7 of 11 cases of carcinoma, in 2 of 12 cases of pancreatitis. The alkaline phosphatose values tended to be higher in patients with carcinoma.

Gastro-intestinal X-rays in 63 cases of carcinoma revealed abnormality worthy of urther study in 69 per cent; 75 per cent of these patients had a non-visualizing gall bladder.

More specific and more selective tests of pancreatic function have yet to be developed.

Kornblueth, Walter; Yardeni-Yaron, Elisheva; and Wertheimer, Ernst. (*Jerusalem*): GLUCOSE UTILIZATION OF THE RETINA. A. M. A. Arch. Ophth. *50*:45-49, July 1953.

The influence of various media on glucose utilization of the retina was studied. Addition of pyruvate, fumarate and glutamate to Krebs-Ringer phosphate solution enhanced appreciably the glucose utilization of the retina, which in this medium reached its highest value. These organic substances could replace bicarbonate. Removal of the calcium from the serum substitute of Krebs increased the glucose utilization of the retina. The same effect was gained if potassium was substituted for sodium.

Leonard, Samuel L. (*Cornell Univ., New York*): GLYCOGEN DEPOSITION IN DIFFERENT SKELETAL MUSCLES INDUCED BY CORTISONE AND ESTRADIOL. Endocrinology *53*:226-32, August 1953.

All skeletal muscles do not respond alike to hormones in depositing glycogen in normal, gonadectomized and hypophysectomized rats of both sexes.

Cortisone increased the glycogen content in rectus femoris but not in cremaster and to greater extent in the rectus of females than in that of males. Estradiol increased glycogen storage in the rectus, abdominal and diaphragm muscles of spayed females but only slightly in the leg muscle of castrated male rats.

Lestradet, H. (*Paris, France*): THE PROBLEM OF DIET IN DIABETICS. Evolution of the Physio-Pathologic Concepts. Therapeutical Inferences. La presse medicale *61*:792-96, June 1953.

In the author's view the classical diet is not only unnecessary but even, to some extent, is undesirable. Only in two particular conditions, does he consider dietetic prescriptions justified: (1) in the obese diabetic and (2) in certain cases of mild diabetes, in which treatment with insulin is not required when a restricted diet is followed.

Lober, Paul H. (*Univ. of Minnesota Dept. of Pathol.*): PATHOGENESIS OF CORONARY SCLEROSIS. A.M.A. Arch. Path. *55*:357-83, May 1953.

The coronary arteries of a series of 536 hearts from autopsies of persons of both sexes from birth to 89 years of age were examined by dissection to determine the severity of atherosclerosis in each. The degree of infiltration of the intima, relative area of lumen, relative thickness of intima, degree of elastic degeneration, and outside diameter of the artery were graded or measured independently and the results tabulated.

The degree of coronary sclerosis was found to increase progressively with age from early childhood through the seventh decade at a nearly uniform rate. Coronary sclerosis was found to be significantly more severe in males than in females, and the degree of coronary atherosclerosis was found to be much greater in hearts with evidence of hypertension than in nonhypertensive hearts from persons of the same age and sex.

Diabetic persons showed more severe coronary sclerosis than others, although not enough cases of diabetes were encountered to supply significant data.

Loewe, Leo; Richmond, Gilbert; Brown, Raymond; Lasser, Richard P.; Cohen, Clifford; and Cox, Harold. (*Jacques Loewe Res. Foundation Labs., Jewish Hosp. Brooklyn, Viral and Ricksettsial Res. Labs., Lederle Labs., Amer. Cyanamid Co.*): THE EFFECT OF REPOSITORY HEPARIN UPON LIPOPROTEIN PATTERNS IN HUMAN BEINGS. Angiology *4*:295-300, August 1953.

Fifty-seven patients were studied; 5 were suffering from conditions other than cardiac or atherosclerotic disease, and no diabetics were listed as such. No changes were made in diet during the study. Repository heparin in doses of 200 to 400 mg. was used, and no difference was noted in the various doses on different patients. The most noted effect was in the S_f 35-100 group; it lasted up to 72 hours with an average of about 24 hours.

Lourau, Marguerite. (*Paris*): MODE OF ACTION OF INSULIN ON THE INTESTINAL ABSORPTION OF GLUCOSE. Comptes rendus hebdomadaires des séances de l'Académie des sciences. *236*:1376-78, March 30, 1953.

Insulin does not modify the permeability of the intestinal mucosa to glucose. It does not accelerate the absorption of glucose when the glycemia is lowered.

Luikart, William M. (*Baton Rouge, La.*): SOME MEDICAL COMPLICATIONS OF DIABETIC ACIDOSIS. New Orleans M. & S. J. *104*:667-70, October 1952.

Peripheral vascular collapse is a rather common complication of severe diabetic acidosis. Myocardial infarction occurs not infrequently. The diabetic state predisposes to early coronary sclerosis; peripheral vascular collapse further diminishes the coronary flow; and hypoglycemia due to overtreatment, of itself, may lead to this complication. Cerebralvascular accidents, for similar reasons, may complicate diabetic acidosis. Thus, it is important to repeat the neurological examination at intervals and at times to repeat the lumbar puncture in comatose patients. Congestive heart failure may occur against a background of pre-existing heart disease, when the myocardial reserve is depressed further by dislocation of electrolytes and nutrients, and it may be precipitated by myocardial infarction or excessive administration of parenteral fluids or both. In this situation the effects of digitalis are somewhat less predictable than usual. Also, the potassium therapy which is so widely used in fraught with added hazard since it has been reported that in the presence of heart failure the renal clearance of potassium is markedly reduced even when the urinary volume is normal.

Lyman, Charles P.; and Leduc, Elizabeth H. (*Dept. of Anat., Harvard Med. Sch., Boston, Mass.*): CHANGES IN BLOOD SUGAR AND TISSUE GLYCOGEN IN THE HAMSTER DURING AROUSAL FROM HIBERNATION. J. Cell. & Comp. Physiol. *41*:471-91, June 1953.

Blood sugar, liver, heart and skeletal muscle glycogen of hamsters in the hibernating and nonhibernating states and during arousal from hibernation were studied by microchemical and histochemical methods. In spite of wide individual variations in each group, hibernating hamsters and nonhibernating hamsters in either cold or warm environments exhibited no significant differences in liver and muscle glycogen. The hibernators, however, were found to have significantly higher levels of heart glycogen, and, unlike other hibernating mammals which have been studied, had a somewhat higher blood sugar than the nonhibernating hamsters. This indicates that a low blood sugar is not a prerequisite of hibernation, as has been previously stated.

During arousal from hibernation there was little change in tissue glycogen levels in the first hour; but subsequently, when body temperature rose rapidly, there was a marked loss of glycogen from liver, muscle and

heart. There were no definite trends in blood sugar changes from the beginning to the end of the waking process. There was usually only a slight rise or fall in blood sugar, well within the limits established for hibernating animals. However, in hamsters in which the blood supply to the liver was cut off by ligation at the beginning of waking, the blood sugar dropped to hypoglycemic levels by the time that the anterior portion of the animal had warmed. The change in muscle glycogen was similar to that found in normal waking hibernators.

Mach, René S. (*Geneva, Switzerland*): FLUID AND ELECTROLYTE BALANCE IN DIABETIC COMA. Acta Medica Scandinavica *146*:42-44, June 30, 1953.

Extracellular dehydration leads to a reduced blood volume (hemoconcentration) with diminished renal blood flow, glomerular filtration rate and urea clearance. This reduction in the circulating fluids causes a drop in arterial pressure with peripheral vascular collapse. The decrease of cellular potassium is not accompanied by hypopotassemia during the period of acidosis and appears to have little influence on the state of the patient. It is only as a result of treatment, at the time when acidosis and dehydration are being cured, that hypopotassemia appears, sometimes accompanied by peripheral muscle paralysis, respiratory muscle weakness with gasping respiration, and myocardial failure.

Mackler, Bruce and Guest, George M. (*Children's Hosp. Res. Foundation and the Dept. of Pediat., Univ. of Cincinnati, Cincinnati, Ohio*): EFFECTS OF ACIDOSIS ON THE METABOLISM OF FRUCTOSE. Am. J. Physiol. *174*:54-56, July 1953.

Intravenous fructose tolerance tests were done on dogs in normal (fasting) states and in states of severe acidosis induced by intravenous perfusions of ammonium chloride solution. Results of these tests indicated that fructose disappeared at the same rate from the blood of nonacidotic animals and acidotic animals due to fructokinase in muscle and liver. Unlike hexokinase, fructokinase phosphorylation is not affected by acidosis.

Results of studies on the metabolism of fructose in blood in vitro indicate that fructokinase is probably absent from blood and that acidosis inhibits the utilization of fructose by blood cells.

Maddock, Robert K.; and Krall, Leo P. (*USPHS Hosp., Norfolk, Va.*): INSULIN REACTIONS; MANIFESTATIONS AND NEED FOR RECOGNITION OF LONG-ACTING INSULIN REACTIONS. A.M.A. Arch. Int. Med., *91*:695-703, June 1953.

The mechanism of insulin reactions is discussed, and simple diagrams showing the two most common types, (1) the "adrenalin-like" and (2) "central-nervous-system type," are presented. This classification is based on the immediate, or trigger, mechanism of the reaction. The "adrenalin-like" reaction, usually caused by fast-acting regular or crystalline insulin, follows a rapid drop in blood sugar level and a resulting increase in circulating epinephrine. The "central-nervous-system type" reaction is usually caused by the slower-acting insulins, such as protamine zinc insulin, and follows slower falls in blood sugar levels. The former type of reaction is easy to detect both by the patient and by trained observers, but the latter type of reaction is frequently undetected by the patient as well as his associates. Eight cases exhibiting a variety of "central-nervous-system type" reaction symptoms are presented. Thorough patient instruction is essential, and the patient's associates must be informed of the probable cause of unusual behavior as well as of the value of remedial glucose. It is vitally important to detect mild early alterations in mood, temperament, judgment or behavior in a patient receiving long-acting insulin, because the patient, even though denying the existence of a reaction, may be in the early stages of a most dangerous type of hypoglycemic reaction.

Majer, Robert G. (*Los Angeles, Calif.*): ABERRANT PANCREATIC TISSUE IN THE WALL OF THE STOMACH. J. Internat. Coll. Surgeons *19*:769-72, June 1953.

A brief review of the different theories as to the origin and nature of aberrant pancreatic tissue in the gastro-intestinal tract is presented. A case is reported in which aberrant pancreatic tissue was removed from the anterior stomach wall and in which there were no symptoms referable to the gastro-intestinal tract.

Marks, Paul L. (*Baton Rouge, La.*): DIABETES MELLITUS; OPHTHALMOLOGICAL ASPECTS. New Orleans M. & S. J. *104*:654-56, October 1952.

Diabetes may affect any of the ocular structures. One manifestation frequently described is recurrent hordeola or even carbuncle of the lid in young unrecognized dia-

betics. Also, there are iris changes including iritis, atrophy, rubeosis and changes in the pupillary border. Another condition of the fundus that should be mentioned is lipemia retinalis which is associated with generalized lipemia. Finally, extraocular muscle palsies have been reported and also asthenopia.

Mayer, J.; and Greenberg, R. M. (*Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.*): HYPERTHERMIA IN HYPOTHALAMIC HYPERPHAGIA. Am. J. Physiol. *173*:523-25, June 1953.

Hypothalamic hyperphagic rats were found to have a significantly higher temperature than either operated non-hyperphagic or non-operated control animals. This phenomenon was shown to be due neither to the state of nutrition of the animals nor to obesity per se nor to a breakdown of the mechanisms regulating body temperature. These results indicate that the hyperthermia is in some way associated with the hyperphagia but is not the result of the hyperphagia, since the elevated temperatures were not eliminated by fasting or by reduced food intake and developed before excess weight was gained. This report indicates animals do not eat to keep warm; hence, it contravenes Brobeck's view that food intake regulation is mediated by the hypothalamic thermoreceptors but is compatible with the glucostatic mechanism of food-intake regulation previously postulated by the authors.

Mayer, Jean. (*Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.*): DECREASED ACTIVITY AND ENERGY BALANCE IN THE HEREDITARY OBESITY-DIABETES SYNDROME OF MICE. Science *117*:504-05, May 8, 1953.

Study of the activity of mice with the hereditary obesity-diabetes syndrome in squirrel-type cages reveals that decrease in activity precedes marked obesity and makes it possible to ascribe to this decrease in activity a role in the etiology of the obesity.

Mayer, Jean. (*Dept. of Nutrition, Harvard Sch. of Public Health, Boston, Mass.*): GLUCOSTATIC MECHANISM OF REGULATION OF FOOD INTAKE. New England J. Med. *249*:13, July 2, 1953.

The author reviews the data concerning the glucostatic mechanism which regulates the amount of food eaten and discusses the mechanism. He believes that appetite in experimental animals is controlled by the level of the blood glucose and especially by its utilization. For variations of blood sugar levels to influence hypothalamic gluco-receptors, glucose must cross the membranes of these cells, which implies phosphorylation through the hexakiase reaction. There appears to be a quantitative relation between glucose utilization and the feeling of hunger. When the peripheral glucose arterial-venous difference was bound to exceed 15 mg. per 100 cc. hunger was never present. When this difference remained near zero for any length of time, hunger was always association.

McCance, R. A.; Prior, K. M.; and Widdowson, E. M. (*London*): RADIOLOGICAL STUDY OF RATE OF PASSAGE OF BROWN AND WHITE BREAD THROUGH THE HUMAN DIGESTIVE TRACT. Brit. J. Nutrition 7:98, 1953. (Abstracted from J.A.M.A. *152*:560, June 6, 1953.)

Six subjects, three men and three women whose ages ranged from 25 to 35 years, took part in this experiment. There were two experimental periods; in one the diet consisted largely of brown bread and in the other, white bread. The passage of the breads through the alimentary tract was studied roentgenologically by the addition of a small quantity of barium sulfate to the bread. The brown bread appeared to stimulate a greater secretion of saliva or of gastric juice or of both than did the white bread. The brown bread was evacuated from the stomach and passed through the small intestine more rapidly than the white. bread. The residue from the brown bread, when in the ileum and in the colon, appeared to be greater than that from the white bread. The residue from the brown bread left the colon 24 hours sooner than that from the white bread.

Moreira, Oromar. DIABETIC COMA AND ITS TREATMENT. Revista da Associaçao Mèdica de Minas Gerais *3*:81-84, June 1952.

After commenting upon the frequency, physiopathology, diagnosis and treatment of diabetic coma, the author relates his own experience founded on 22 comas in 536 diabetics.

Mukherjee, Surath Kumar. (*Calcutta, India*): STUDY OF A NEW MODIFIED INSULIN (Type NPH). Indian Medical Gazette *87*:516-17, November 1952.

Moderately severe stable diabetes was found to be effectively controlled for a twenty-four-hour period on a single injection of NPH insulin prior to breakfast. The important adjuncts for uniform result are a suitably timed dietary regimen and an effective dosage of the insulin.

Murphy, E. S. (*Missoula, Mont.*): DIABETIC RETINOPATHY. Rocky Mountain M. J. 50:562-64, July 1953.

The author reviews the nature and treatment of retinal changes in diabetes.

Musser, Marc J.; Lorenz, Thomas H.; and Derus, Gerald J. (*Madison, Wis.*): HYPERVENTILATION AND PSEUDOHYPOGLYCEMIC REACTIONS IN DIABETES MELLITUS. J.A.M.A. *152*:1113-16, July 18, 1953.

The data presented show that, in certain diabetic patients, reactions simulating mild to moderate hypoglycemia occurred as a result of hyperventilation. Thus, hyperventilation as well as cerebral dysrhythmia provides an explanation for pseudohypoglycemic reactions occurring in diabetes mellitus. The successful management of such diabetic patients entails appropriate psychotherapy and correction of their faulty breathing pattern under stress, in addition to the usual medical measures.

Detailed study of 14 diabetic patients who were having frequent "insulin reactions" revealed the following facts: 1. Reactions that were not accompanied by hypoglycemia occurred quite commonly in this group. 2. All the patients were excessively anxious and also were hyperreactive to two minutes of hyperventilation. 3. The symptom incurred by overbreathing reproduced in these patients their typical symptoms of "insulin reactions." 4. None of the patients had electroencephalographic evidence of cerebral dysrhythmia (even with hyperventilation). It is concluded that when the hyperventilation syndrome occurs in anxious diabetic patients, it can produce symptoms that stimulate, and thus are easily misinterpreted as, true insulin reactions.

Nadeau, Guy; and Rouleau, Yves. (*Hosp. Saint-Michel-Archange, Mastal, Quebec, Canada*): INSULIN TOLERANCE IN SCHIZOPHRENIA. J. Clin. & Exper. Psychopathol. *14*:69-77, June 1953.

Most of the schizophrenics in the group studied showed a definite delayed response to insulin as well as to an induced hypoglycemia during the insulin tolerance test (I.T.T.). No consistent correlation could be observed (a) between the response to insulin during the I.T.T. and the average coma dose necessary to induce coma during shock therapy and (b) between the hypoglycemic response and the length of the coma. When glucose-insulin-tolerance tests (G.I.T.T.) were preformed on the same subjects, the response to insulin as well as to the induced hypoglycemia was normal. The overcompensatory effect of the antagonists to insulin during the fasting state in certain schizophrenics is probably set aside during the primary hyperglycemic phase of the test, so that the insulin can exert its effect without inhibition. The peculiar behavior of the authors' group under insulin stimulation agrees with the theory of horomonal imbalance in the etiology of most of the schizophrenias. Such dyshormonism is characterized by an overresponsiveness on part of the adrenals.

Oppenheimer, Henry E. (*St. Louis Univ., St. Louis, Mo.*): THE RELATION OF OBESITY AND AGE TO INSULIN IN A DIABETES CLINIC. M. Bull. Saint Louis Univ. 5:27-29, February 1953.

Age and weight studies were made of a representative group of 153 diabetics in the Firmin Desloge Hospital outpatient department to determine whether a correlation existed between the different types of diabetes and insulin therapy. It was determined that the most obese and the oldest diabetics required no insulin and that, when there was a history of less obesity and an earlier onset of diabetes in life, progressively greater doses were required. It is believed that a certain number of patients could have their insulin eliminated with more adequate dietary control. The factors which impede this have been enumerated.

Ottaway, J. H. (*Univ. Coll., London*): THE INSULIN-LIKE ACTION OF GROWTH HORMONE. Brit. M. J. 2:357-59, August 15, 1953.

A Warburg flask study under rather rigid controls demonstrated an increased glucose uptake in normal rat diaphragm with growth hormone added and in alloxan-dia-

betic rats with growth hormone and insulin. It did not occur in alloxan rats not previously injected with insulin.

Patterson, John W. (*Western Reserve Sch. of Med., Cleveland, Ohio*): CATARACTS CAUSED BY CARBOHYDRATES. Am. J. Ophth. *36*:143-49, June 1953.

It has been shown that galactose and glucose act in a synergistic fashion in the production of cataracts, and this has been interpreted as indicating that they produce their effect in a common manner. Ascorbic acid injected intravenously as dehydroascorbic acid and phosphate added to the drinking fluid failed to delay the development of diabetic cataracts. Rats placed on a 35 per cent galactose diet for four days of each week and starved three days of the week developed cataracts in an average of 40 days. Rats on an identical galactose regime but receiving a supplement of normal diet instead of being starved three days each week did not develop cataracts. This was interpreted as indicating that carbohydrate cataracts were the result of a metabolic deficiency that could be corrected by providing the proper supplement at a time when the cellular absorption mechanisms were not blocked by a high sugar level.

Pickard, Karl; Kelter, Joseph J.; and Rothenberg, Robert E. (*Cent. Med. Group, Brooklyn, N. Y.*): ISLET CELL TUMOR OF THE PANCREAS WITH SURGICAL CURE. Ann. Int. Med. *38*:1306-13, June 1953.

A case of severe hyperinsulinism due to a functioning pancreatic adenoma is reported. The patient presented marked hypoglycemic symptoms with convulsions, marked personality changes with infantile regression and evidence of an old myocardial infarction. He made a complete recovery following surgical removal of the tumor. Surgical exploration is advocated in all cases of pronounced hyperinsulinism, particularly in the absence of hypopituitarism or adrenal hypocorticism.

Queries and Minor Notes (*Alpena, Mich.*): DRENCHING NIGHT SWEATS. J.A.M.A. *152*:483, May 30, 1953.

In any diabetic patient taking insulin, hypoglycemia or a rapidly falling blood sugar level must be considered as a possible cause of sweating. Sweating is an unusual symptom in diabetes, but, in less aggravated form than that described by the questioner, it is occasionally encountered both generally and locally. In one instance sympathectomy was done for sweating arm. Apart from the causes of sweating in diabetes, the common causes of hyperhidrosis must be considered. These are chronic febrile conditions, hyperthyroidism and nervous or emotional strain and lability. Often patients with labile diabetes are also unstable from the standpoint of the nervous system, with overactivity of the sympathetic component. In emotionally labile persons, administration of phenobarbital in small doses together with belladonna, atropine or methantheline (Banthine) may be of help.

Queries and Minor Notes (*Baltimore, Md.*): NECROBIOSIS LIPOIDICA DIABETICORUM. J.A.M.A. *152*:985, July 4, 1953.

Treatment of necrobiosis lipoidica by surgical excision and skin grafting has been carried out in so few cases that relatively little information is available for guidance. If conservative measures are employed, lesions usually heal with the formation of a thin, cellophane-like covering. After such healing, no disability other than disfigurement results. In any case, if surgery is contemplated, any superimposed infection should be controlled and excision made with a relatively wide margin to insure postoperative healing and success of grafting.

Queries and Minor Notes (*New York*): SECONDARY GLAUCOMA. J.A.M.A. *152*:655, June 13, 1953.

The secondary glaucoma caused by rubeosis iridis constitutes the most difficult problem in the management of glaucomas. There is no medical treatment of value; the pain caused by the condition commonly leads to enucleation, which is the procedure preferred. Palliative surgical therapy, such as cyclodiathermy, may be useful in controlling pain and perhaps intraocular pressure but will not restore vision. The retrobulbar injection of alcohol may also be of some value in relieving pain. If the eye is not painful, no treatment is indicated.

Queries and Minor Notes—Bolinske, Robert E. (*Clintonville, Wis.*): CARE OF INFANT OF A DIABETIC MOTHER. J.A.M.A. *152*:105, May 2, 1953.

Adequate control of the mother's diabetes during pregnancy will greatly reduce mortality among the newborn. The mother should be given adequate insulin therapy during delivery. The infant should receive 10 cc. of 5 per cent dextrose in water by mouth immediately after birth and then every one or two hours during the first few days in addition to his regular feedings. Five cubic centimeters of 5 per cent dextrose in sodium chloride solution may be injected in each buttock if it is not taken by mouth. Other authorities recommend administration of 20 to 30 cc. of 5 per cent lactose solution by medicine dropper every two hours for the first few days of life.

Queries and Minor Notes—Dolger, Henry (*New York*): ALLERGY TO INSULIN. J.A.M.A. *152*:296, May 16, 1953.

Local cutaneous reactions that follow insulin injection can be prevented or minimized by the addition of 0.1 cc. of chlorprophenpyridamine (Chlor-trimeton) maleate solution (100 mg. per cc.) to the syringe containing the usual dose of any form of insulin. The entire mixture is then injected in the ordinary manner. In the presence of generalized allergic reactions to insulin, denatured insulin may be resorted to. The immersion of a vial of crystalline zinc insulin in boiling water for 30 minutes reduces its antigenicity without appreciably reducing its physiological activity. After the boiled insulin has been administered one, two, or three times daily, as needed, for about two weeks, ordinary commercial protamine or isophane (NPH) insulin usually may be substituted, without inducing further allergic response.

Queries and Minor Notes—Gifford, John P. (*Vero Beach, Fla.*): SIMULTANEOUS ADMINISTRATION. J.A.M.A. *152*:296, May 16, 1953.

There is no objection to the simultaneous administration of 5 per cent glucose in sodium chloride solution and citrated blood or of isotonic sodium chloride solution with citrated blood. This is often done in many hospitals with no bad side-effects. The important point to remember is that all solutions must be isotonic and pyrogen-free.

Queries and Minor Notes—Jones, W. W. (*Jordon Valley, Ore.*): UNDERNUTRITION TREATMENT OF DIABETES MELLITUS. J.A.M.A. *152*:295, May 16, 1953.

Dr. Fredrick M. Allen was responsible for the development and wide usefulness of the method of treating diabetes mellitus by undernutrition. It is a sound and practical method, which operates by correction of obesity, lowering of metabolism and improvement of tolerance for sugar under those conditions. The field of usefulness of undernutrition in treatment of diabetes is no longer as broad as it was. The discovery and common use of insulin has narrowed its practical application. However, in the mild and obese diabetic, it has fundamental value, which has been neglected since insulin has become available. Too few physicians know and have proper respect for it.

Queries and Minor Notes—Milton, J. S. (*Minneapolis, Minn.*): AMPHETAMINE AND BLOOD SUGAR. J.A.M.A. *152*:294, May 16, 1953.

The effect of amphetamine (benzedrine) sulfate and dextroamphetamine (dexedrine) sulfate on the blood sugar has been studied in a number of investigations, usually as incidental observations. It has been the consensus of reports in the American literature that these drugs have little or no effect on the blood sugar.

Rausch-Strooman, J.-G.; and Sauer, Heinrich (*Univ. Clin., Hamburg-Eppendorf, Germany*): ON THE QUESTION OF INSULIN RESISTANCE THROUGH ANTIBODY FORMATION. Klinische Wochenschrift *31*:551-55, June 15, 1953.

A group of rabbits was treated with an insulin adjuvant complex. Thereupon one-half of the animals became relatively insulin resistant, probably as a result of the formation of neutralizing antibodies against insulin albumin. In favor of this is the positive result of the complement binding reaction made with insulin as an antigen. These findings are discussed with a view to the insulin therapy and the special question of whether admixture of unspecific albumin in the insulin preparation could increase the formation of antibodies against the insulin itself.

Revitch, Eugene (*Veterans Admin. Hosp., Lyons, N. J.*): MANIFESTATIONS OF HYPOGLYCEMIA AND THEIR RELATION TO BLOOD SUGAR LEVELS. J. M. Soc. New Jersey *49*:515-19, December 1952.

Hypoglycemic manifestations can be divided into five stages which are delineated by the author. The physi-

ologic basis for this is the "dissolution" of the central nervous system. Hypoglycemia depresses various levels of the nervous system through anoxia, since carbohydrates are the only source of energy utilized by the brain. The higher levels of the nervous system are depressed earlier because their metabolic requirements are greater. No direct relationship between the blood sugar level and hypoglycemic manifestations could be found. The explanation of hypoglycemic reactions resides in the functional impairment of various levels of the central nervous system due to focal anoxia. Clinical experience shows that, depending on the functional state of the central nervous system, various levels of blood sugar will be needed for proper oxygen utilization by the brain.

Ricketts, Henry T. (*Chicago, Ill.*): THE MODERN TREATMENT OF DIABETES MELLITUS. J. Kentucky M. A. 50:429-32, October 1952.

The objectives of treatment in diabetes are for the most part attainable by careful attention to diet and insulin so that the blood and urine sugar are controlled as strictly as the avoidance of hypoglycemia will permit.

Simpson, N. R. W.; and Trowbridge, G. F. (*Leicester Royal Infirmary and Gloucester Royal Hosp., England*): FATAL COMPLICATION FOLLOWING INSULIN THERAPY IN RHEUMATOID ARTHRITIS. Ann. Rheumat. Dis. *12*: 142-43, June 1953.

A case is reported of a patient who appeared to die in an insulin-resistant diabetic coma after two courses of insulin therapy for rheumatoid arthritis. Eight thousand units of insulin in 30 hours had no effect. Cerebral and pulmonary edema and edema of the connective tissue were found postmortem. It would appear unlikely that a diabetes of this type would be due to the production of ACTH by insulin therapy. The coma, due to depression of endogenous insulin production, should have reacted to the large doses of insulin. No record of a similar case could be found in the literature.

Van Itallie, Theodore B.; Beaudoin, Rachel; and Mayer, J. (*Dept. of Nutrition, Harvard Univ. Sch. of Public Health, and Med. & Surg. Clin., Peter Bent Brigham Hosp., Boston*): ARTERIOVENOUS GLUCOSE DIFFERENCES, METABOLIC HYPOGLYCEMIA AND FOOD INTAKE IN MAN. J. Clin. Nutrition *1*:208-17, March 1953.

Blood sugar studies were done on six adult human subjects under either "metabolic balance" conditions or under conditions in which food intake was carefully recorded. Six experimental situations were investigated: (1) constant adequate caloric intake, (2) constant inadequate caloric intake, (3) uncontrolled diabetes mellitus, (4) cortisone administration, (5) low-fat diet, and (6) epinephrine administration. An attempt was made to correlate various dietary regimens, arteriovenous glucose differences ($\triangle$-glucose), and presence or absence of an urge to eat. In normal subjects, values for $\triangle$-glucose throughout the day generally reflected the previous dietary intake. A submaintenance caloric intake was associated with a small $\triangle$-glucose area and an adequate caloric intake with a normal $\triangle$-glucose area. Cortisone administration was followed by hyperglycemia but a smaller than normal $\triangle$-glucose area. The effect of cortisone on food intake was interpreted in the light of this finding. It is believed that consideration of the antecubital $\triangle$-glucose area as an index of glucose assimilation by peripheral tissues permits application of the glucostatic theory to conditions associated with impaired carbohydrate utilization.

Wilkey, J. Lester; Nora, Ernest; Lagorio, Frank A.; and Barson, Lloyd J. (*Columbus Hosp., Chicago, Ill.*): ACUTE NECROTIZING PANCREATITIS AND LOWER NEPHRON SYNDROME FOLLOWING TRANSURETHRAL PROSTATIC RESECTION. J. Internat. Coll. Surgeons *19*:322-26, March 1953.

A case of acute necrotizing pancreatitis and lower nephron syndrome following transurethral resection is presented. The possibility of a common etiologic agent in the two pathologic conditions is considered and discussed. This is the fourth case report in the world literature.

Williams, Matthew A.; Friedberg, Felix; and Marshall, Lawrence M. (*Dept. of Biochemistry, Coll. of Med., Howard Univ., Washington, D. C.* NONFIXATION OF CARBON DIOXIDE INTO ORGANIC ACIDS IN BLOOD. Science *117*:502-04, May 8, 1953.

On the basis of chromatographic isolation of labeled organic acids from tissues and blood of mice after intraperitoneal injection of labeled bicarbonate, the authors report a fixation of the carbon into organic acids in the liver and, to lesser degree, in the kidney and in muscle, but the blood lacks mechanisms for synthesis of organic acid from labeled bicarbonate, and the organic acids present in blood slowly diffuse into it, especially from the liver.

EDITORIALS

THE INFLUENCE OF INSULIN ON PROTEIN METABOLISM

Since various opinions have been expressed about the part played by insulin in protein metabolism, it is fitting to review some of the literature to see how these different conclusions may be explained. Table I presents a summary of selected articles of which some are old and often quoted, and others permit one to think of the most recent methods and results in this field. The table indicates some of the main headings although no such simplified arrangement does justice to such a variety of experimental detail.

It is clear that the exaggerated protein metabolism of pancreatectomy or severe diabetes mellitus and the control of this accelerated protein catabolism by insulin have been consistently observed[1–5] since the epoch-making works of von Mering and Minkowski[6] and Banting and Best[7]. There is no question about the fact that, when used to replace severe insulin deficiency, insulin has a powerful protein anabolic action within certain limits. "Within limits" means that protein metabolism is restored to normal, but that (except for the transitory restoration of the protein deficit) there is no sustained anabolism above and beyond the normal level of protein balance.

In contrast to the depancreatized animal, the results in Houssay animals may be noted. The actual fasting nitrogen excretion is the same in the normal animal and in the Houssay animal which lacks both pituitary and pancreas. One would conclude from this that insulin does not influence protein metabolism in any primary or direct manner, a conclusion which would be quite at variance with the striking effect of insulin in the diabetic animal. Both phenomena force one to think of the metabolic situation in which insulin is acting. In any case, the tendency of insulin to restore the protein balance of diabetic animals to, but not beyond, the normal equilibrium has been further examined by the use of insulin in normal animals and man. It is here, i.e., in the normal animal, that some difference of opinion has arisen. Without analyzing all of the experiments, one may note certain features of the experiments listed in Table I under the heading, "Investigators who failed to observe protein anabolism."

In the first place, some of these experiments were conducted in fasted animals. There seems to be complete agreement that the administration of insulin does not cause demonstrable protein anabolism in the fasted animal [1, 8, 9, 10]. This is compatible with other observations on protein anabolism. Thus, Munro[11] reviews the caloric requirements for protein storage under various conditions and concludes that the addition of extra energy to an adequate diet usually leads to nitrogen retention whether this energy is provided by carbohydrate or fat. Moreover, the feeding of carbohydrate to fasting animals reduces the nitrogen output, but the feeding of fat does not have this effect until the fat stores are exhausted. If these things are so in normal animals with ample endogenous insulin, one would not expect protein anabolism to take place when insulin was added during the fasting state. Even insulin cannot make bricks without straw. These comments on protein metabolism during fasting may be concluded by noting an important difference between insulin and growth hormone. Growth hormone has a nitrogen sparing action in the fasting normal animal[12, 13]. With this effect on protein there is a mobilization of fat, which is manifested by increased ketonuria and also[14, 15] by a diminution in body fat.

Another point about these experiments (Table I, II, A) is that in some of them[9, 16, 17] one dose of regular insulin was given daily, sometimes followed by the observation of urinary nitrogen for a few hours only. It now seems, from many studies on nitrogen excretion, from studies with repeated doses of insulin or protamine insulin, and from current knowledge of the cumulative action of growth hormone[18, 19] that the conditions which lead to protein anabolism are the ones in which there

TABLE 1

Selected studies of the influence of insulin on protein metabolism

I. Pancreatectomy results in an increased catabolism of endogenous protein (increased N excretion during fasting)[6].
Insulin treatment of depancreatized animal, or of severe diabetic patient, prevents this "secondary" acceleration of protein catabolism[1–5].

II. Insulin given to normal animals

A. Investigators who failed to observe protein anabolism:
No increased growth of rabbits[16].
No effect on fasting N balance of rats[8].
No effect on growth or N excretion of normal rats, with or without control of diet[9].
No change or an increase in N excretion[17].
Increased N excretion of fasting dogs[1].
No effect on growth of rats[25–27].
No effect on protein depletion or repletion[10].

B. Investigators who concluded that insulin promotes protein anabolism:
Glucose and insulin spare more protein than glucose alone in normal subjects[20].
Insulin causes positive N balance in fed normal dogs[1].
Insulin causes nitrogen retention in normal rats, with or without constant diet[21].
Positive N balance in patients given insulin (appetite increased)[22].
Insulin reduces accumulation of blood NPN in nephrectomized dogs[23].
Liver and diaphragm incorporate more labeled amino acid under influence of insulin if glucose is present[24].

III. Relation of insulin to the action of other hormones on protein metabolism

A. Testosterone (T)
No effect of T on blood NPN in depancreatized dogs[29].
Anabolic effect of T occurs in alloxan diabetic rat[30].
Ability of T to increase arginase activity of kidney was not impaired in alloxan diabetes[31].
T causes N retention in hypophysectomized rats on constant diet[32,33].

B. Growth Hormone (GH)
Action is impaired in insulin deficiency[34].
Nitrogen retention in fasting rats[12,13].
Lability of nitrogen of different muscles varies under influence of GH or inanition[45].
Effect of GH on special tissues[46].
Part of defective growth of hypophysectomized rats was restored by forced feeding[38].
GH caused N retention in diabetic rats, but no N retention in Houssay cats[35–37].
Insulin causes growth in hypophysectomized rats[28].
Extended protein repletion in rats[10].

C. Adrenal Cortical Hormones
Effect of cortisone on protein of different tissues[47].
Insulin does not prevent the increased N excretion caused by cortisone or ACTH[40–41].
Increased insulin seemed to prevent or reduce increased N excretion in diabetics receiving ACTH[42].

D. Excess catabolism of hyperthyroidism and growth promoting action of thyroid hormone in cretinism both occur in presence of ample insulin (the thyroid is not discussed herein).

is a fairly sustained action of the anabolic influence.

The next group of experiments (Table I, II, B) provides definite evidence that in the fed animal or man, insulin tends to cause protein anabolism as measured by nitrogen balance[1, 20, 21, 22] or by other methods [23, 24]. The tendency of insulin to produce a positive nitrogen balance has not led to growth in normal animals[25–27] and with the exception of the report of Salter and Best[28] which will be discussed later, there is no evidence that insulin influences growth as shown by the tibia test. Probably the physician has seen the most striking failure of insulin to produce growth in the case of patients with islet cell adenomas. Some of these people have had hypoglycemia for years before operation; some are thin, many slightly obese; but none have ever had excessive growth of the type seen in acromegaly. Whatever the reason for this may be, these patients show us that the anabolic influence of insulin does not of itself suffice for body growth, however important it may be as a synergist to growth hormone.

It is probable that a study of the relation of insulin to the action of other hormones which promote protein anabolism is essential to an understanding of the action of insulin itself (Table I, III). In the case of testosterone, more information is required to define its relation to other anabolic agents. The evidence of Sirek and Best[29] indicates that insulin is required for the anabolic action of testosterone, since there was no alteration of the blood NPN by testosterone in depancreatized dogs deprived of insulin. The studies of Kochakian[30, 31] do not contradict this because the presence of insulin is not excluded by our present methods of producing diabetes in rats. For the moment, one must conclude that the presence of insulin, but not necessarily its increased secretion, is required for the action of testosterone on protein metabolism. In contrast to this, testosterone causes nitrogen retention in the absence of growth hormone, i.e., in the hypophysectomized animal[32, 33]. Although this is a concise statement, the biochemical sites of action of all hormones which regulate protein metabolism are quite obscure.

The relation of insulin to anterior pituitary growth hormone has been studied for years by the use of crude and later of highly purified preparations with growth-promoting activity. Thus, it has been determined that in depancreatized dogs and cats maintained on fixed doses of insulin, the action of growth hormone on nitrogen balance is present but greatly reduced[34, 35]. Nitrogen retention also takes place when growth hormone is given to alloxan diabetic rats whose available

insulin is obviously reduced[36, 37]. More recently, the effect of one hormone in the absence of the other has been examined. Milman *et al.*[35], using metabolic periods in hypophysectomized-depancreatized (Houssay) cats found that in the absence of insulin, growth hormone caused no retention of nitrogen. Since growth hormone is most accurately tested in hypophysectomized animals, this result cannot be due to the pituitary deficiency, and the essential part played by insulin in the anabolic action of growth hormone is apparent.

On the other hand, the determination of the effect of insulin on protein metabolism in the absence of growth hormone is only beginning to receive attention. The absence of growth hormone means the use of the hypophysectomized animal which, as is well known, is extremely sensitive to insulin. Nevertheless, Salter and Best[28] have described growth in hypophysectomized rats treated with protamine insulin. The tendency of hypophysectomized rats to continue growing up to 40 days of age was duly controlled. Growth was measured by body weight, body length and the tibia test, and there is no doubt about the fact that growth occurred. However, there is still doubt about the mechanism by which this growth was produced. The impaired growth after hypophysectomy is observed in the presence of ample insulin and of insulin sensitivity but on a reduced food intake. The protamine insulin which was used increased the appetite of the treated rats which were also given additional food or glucose to prevent or treat insulin reactions. Samuels *et al.*[38] restored part of the defective growth of hypophysectomized rats by forced feeding. For this reason it is uncertain whether the results of Salter and Best[28] were due to some primary action of insulin or to the secondary effect of the increased food intake.

During the past year Doctor McCann and I have done preliminary experiments related to this problem. On a constant diet of meat, the nitrogen excretion of cats was recorded. When 5 to 10 grams of glucose were added daily to the meat diet, the usual protein sparing action of carbohydrate was observed, as nitrogen retention, in the normal animals (Tables 2 and 3). *In hypophysectomized cats treated in a similar manner, there was no protein sparing effect of carbohydrate.* These experiments were designed to test the effect of the endogenous insulin which is presumably secreted in response to the added glucose and, at the same time, to avoid the hazard of insulin reaction. The results in cats differ from those in rats in which Bancroft, Geiger and Hagerty[37] found that the nitrogen sparing action of sugar was of the same magnitude in normal and in hypophysectomized animals. This indicates that one must reckon with a striking species difference in such experiments.

TABLE 2

The effect of operative procedures on pancreatic diabetes in the cat[39]

Type and No. of Cats	Urine			Liver fatty acids per cent
	Glucose g/k/d*	Nitrogen g/k/d*	Ketones mg/k/d*	
Normal (7)	0	0.6	15	5
Depancreatized (10)	3.2	1.4	133	24
Hypox-depan. (6)	0.7	0.7	8	9
Adrex-depan. (14)	0.5	0.7	10	7

* Fasting values—gm. or mg. per kilo per day.

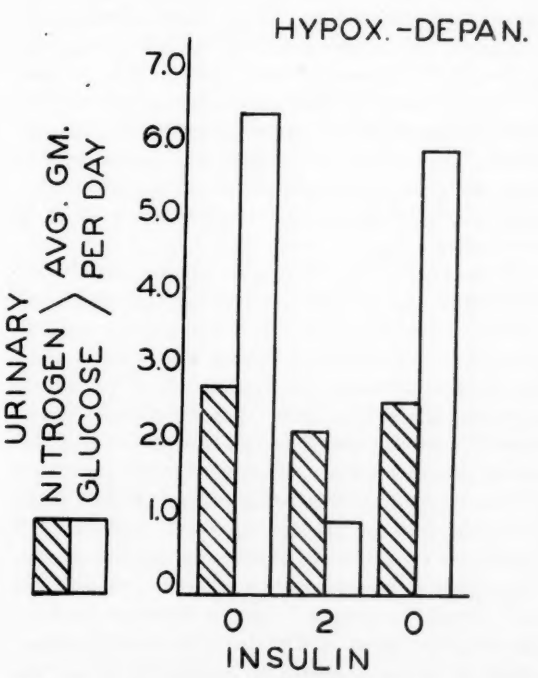

FIGURE 1. Cat 6-53. Hypophysectomized March 4; depancreatized, April 6, 1953. Diet of 50 gm. of meat and pancreatic extract (Viokase) was constant throughout the periods charted. These periods were consecutive and consisted of a control period of 5 days, a middle period of 5 days when 2 units of protamine insulin was given daily, and an after-period of 4 days without insulin. The effect of insulin on the glycosuria is obvious; the effect on the nitrogen excretion is significant. The difference between the nitrogen excretion of the second control period and the insulin period is 0.38 gm. per day. This corresponds to the average nitrogen retention observed when 5 gm. of glucose was added to the diet of the normal cat (cf. Table 3).

TABLE 3
Protein sparing action of carbohydrate in cats

Cats Type	No.	Average Urinary Nitrogen: Meat[1] only gm/day	Meat plus glucose gm/day	Average nitrogen retained gm/day
Normal	10	3.55±0.11	3.16±0.13	—0.39±0.06
Hypox.	5	2.89±0.26	2.97±0.26	+0.08±0.12

[1] The amount of meat (100 gm. daily) was constant throughout all periods.

We have tested the effect of insulin in a single Houssay animal (Figure 1). Compared to control periods before and afterward on a constant diet, insulin brought about the utilization of 5 gm. of urinary glucose. This was accompanied by a significant diminution in nitrogen excretion. If this single experiment is confirmed, the situation will be as follows. Glucose spares protein in the normal cat; glucose fails to spare protein in the hypophysectomized cat; glucose utilized by administered insulin spares protein in the Houssay animal. This means that glucose and insulin may or may not spare protein when the pituitary is absent. Such a result suggests that better methods of assay are needed.

Little is known of the relation between insulin and the adrenal cortical hormones, yet this is a large component of the subject of insulin and protein metabolism. Long and Lukens[39] showed that adrenalectomy abolished the protein catabolic response to pancreatectomy and many investigators (e.g.[40, 41]) have demonstrated the protein catabolic action of ACTH and cortisone under various conditions. However, the effect of insulin on the protein catabolic action of the adrenal cortical hormones has received less attention. Ingle *et al.*[40] and Conn *et al.*[41] found that in the rat and in man large doses of insulin which reduced the glycosuria did not control the increased nitrogen excretion produced by cortisone or ACTH. On the other hand, increased doses of insulin appeared to prevent or reduce the increased N excretion in diabetic patients who were receiving ACTH[42] but here the picture is complicated by the simultaneous relief of the complicating rheumatic disease. All these possibilities are well discussed in the study of Burns *et al.*[49] who found that cortisone did not alter the response to insulin in the fasting state but strikingly altered the glucose-insulin test.

The failure of insulin to produce growth in normal animals or in patients with islet cell tumors might be due to the antagonistic action of the adrenals. If this were so, it might explain why, in spite of these results in the normal animal, Salter and Best[28] observed growth in their hypophysectomized rats which lacked the normal degree of adrenal cortical function.

It is with an eye to the future that certain studies on protein metabolism should be particularly noted. The importance of the quantity and quality of the protein intake, the relation between caloric intake and protein storage and the need for differentiating the effects of the anabolic hormones which may be acting simultaneously are fairly well recognized. In addition, there are features of protein metabolism which may point the way to the development of better methods.

The procedures most commonly used to study protein metabolism have included the measurement of dietary, urinary and fecal nitrogen; body growth; changes in the protein or nitrogen content of the carcass; changes in the rate of accumulation of the nitrogenous constituents of the blood in nephrectomized animals. All of these record the systemic equilibrium or response and all are affected by both dietary and hormonal factors. If, in agreement with Handler[50], one calls growth hormone, testosterone, thyroxine and insulin the anabolic hormones, it is already clear that they act in different ways even if considerable synergism is involved. How are we to identify more accurately these sites of action on protein metabolism? First, we should make more use of the response of individual tissues with the hope of selecting the most significant site of action of the metabolic hormones. In 1936, Addis, Poo and Lew[43] examined the rate of protein formation in numerous tissues of the body after depletion and re-feeding. They concluded that, "each organ and tissue has its own individual characteristics with respect to the degree and rate of the rebuilding of protein when casein is given after a period of protein loss" (see Figure 2) and recorded appropriate details. Munro and Naismith[44] have made similar observations relevant to the influence of energy intake on protein metabolism, and they call attention to "the bodily distribution of changes in nitrogen balance." Geiger *et al.*[45] found no effect of insulin, growth hormone or cortisone on the gain in body weight during repletion.

This provides an interesting background to the current reports of Greenbaum and Young[46] and Scow[47]. The former[48] compared the loss of nitrogen in various tissues during inanition and the gain in tissue nitrogen during treatment with purified growth hormone. In particular, the striking lability of the nitrogen content of certain muscles and the relative stability of other

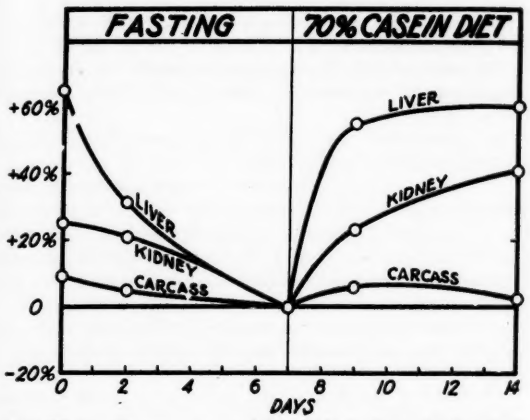

FIGURE 2. Changes in protein content from levels at 7-day fast. From: Addis, Poo and Lew: J. Biol. Chem. 116:343, 1936

muscles was noted. Scow[47] observed the effect of growth hormone on various protein fractions in the muscles of thyroidectomized and hypophysectomized rats. As an example of his results, growth hormone promoted a marked weight increase in the thigh muscle, accompanied by a significant increase in the myosin fraction. This agrees with Greenbaum and Young's[46] finding that the quadriceps was a most active and "labile" muscle in regard to changing its nitrogen content. The individual characteristics of different tissues has also been demonstrated in the response of rats to cortisone which caused a wastage of nitrogen from carcass fractions other than structural protein (i.e. collagen and elastin)[48]. The protein of the liver was increased by this so-called catabolic hormone, indicating that a re-distribution of protein may take place within the overall protein balance. The sites and nature of protein anabolism induced by testosterone have also been described[49]. In summary, if the tissues and the particular proteins which are influenced by the hormones can be identified, there should be better methods of assaying their action.

SUMMARY

Insulin promotes protein anabolism secondarily by its action on the utilization of carbohydrate in the presence of other anabolic hormones. The following facts appear to support this concept.

(a) Insulin does not cause nitrogen retention in the fasting animal (in contrast to growth hormone).

(b) The protein sparing power of carbohydrate.

(c) The quantitative relations between caloric intake and protein anabolism in normal animals.

(d) Additional insulin, administered or from a secreting islet cell tumor, does not cause growth, in spite of a definite tendency to nitrogen retention.

(e) Insulin, *as replacement therapy,* prevents or improves diabetic dwarfism and prevents the catabolic response to pancreatectomy.

(f) Since the protein catabolic response of pancreatic diabetes is abolished by removing the pituitary or adrenal glands to the same degree as when insulin is given, insulin would not appear to have a primary or direct action on protein metabolism.

(g) As noted, in all of these conditions other anabolic hormones, notably growth hormone, are present.

(h) The failure of normal growth in the hypophysectomized animal takes place in the presence of endogenous insulin which may cause added fat formation. It is in part corrected by forced feeding. Such added factors as age and possibly species which influence the degree to which hypophysectomized animals may grow, must be considered.

Possibly discrepant facts are: (1) the administration of insulin causes true growth in rats (certain questions of diet and species behavior may need elucidation) and (2) the nitrogen retaining effect of insulin in the Houssay animal (one experiment only).

In conclusion, a review of these studies on the influence of insulin in protein metabolism suggests that we should examine the effects of anabolic hormones on specific tissues, on particular proteins of those tissues and probably on the accelerated incorporation of labelled amino acids into such selected proteins in the hope of improving methods of assay which at present permit considerable discrepancies to appear.

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NUTRITIONAL ADEQUACY OF THE DIABETIC DIET

Advances in medicine have enabled the physician to reduce the mortality rate from diabetes mellitus. The introduction of insulin therapy, the understanding of fluid and electrolyte balance in the treatment of ketotic acidotic coma and the use of sulfa drugs and antibiotics were the contributing factors to this increased longevity. One of the major problems that remains is the avoidance of chronic invalidism of those whose lives have been extended. The treatment of a chronic disease should be designed to allow the individual to make his full contribution to society. The mere prolongation of life without health or happiness is short of the desired goal.

In the maintenance of good health and a sense of well-being, the *adequacy of the nutrition* of the individual is a very important factor. The term "adequate" is relative and its interpretation very variable. A diet adequate for a healthy young, vigorous adult male is excessive for a female or an elderly male. At the same time, it may be inadequate for a growing boy or in the rehabilitation convalescent period of the young adult. The problem is to define a set of nutritional requirements for the diabetic and teach the physician to calculate the diets accordingly.

A great many dietary standards have been promulgated for population groups and even for individuals. In 1940 the Food and Nutrition Board of the National Research Council accepted the responsibility for developing a dietary standard for the people of the United States. The philosophy of their recommendations was based on *allowances suitable for the achievement of good nutrition in the whole population* rather than filling the minimal needs of the average individual. These were published in 1943, and revised in 1945 and again in 1948. They are at present undergoing further revisions in certain detail.

It is universally accepted that diet therapy is the keystone to modern treatment of diabetes mellitus. The accent of the diet therapy has been on the control of one very obvious phase of the condition, that is carbohydrate utilization and prevention of hyperglycemia and glycosuria. This emphasis at times has distracted attention from the over-all nutritional adequacy of the diet. In the published literature in this field, frequent reference is made in the text of an article to the importance of nutrition. Examination of the tables and figures of diets actually prescribed not infrequently fail to substantiate the text. The statement, "If the weight is maintained, the diet is adequate in calories," is commonly quoted. An analysis of this statement proves its incompleteness. The statement should read "If the *ideal or optimum* weight is maintained, the diet is adequate in calories." Reduced caloric intakes result in adaptative mechanisms with associated lowering of metabolic requirements and slowing down of metabolic processes. Caloric equilibrium can be reached and body weight maintained at a 1200 to 1500-caloric intake for a young adult whose optimum calorie requirement may be 2600 calories. At the lower equilibrium, he is incapable of a full active, healthy life and will show easy fatigibility, decreased resistance to infection, loss of vigor, and even apathy and mental depression. At the higher level of a caloric equilibration, he can be a normal adult with a sense of well-being.

The most commonly prescribed diets for diabetic adults today (Table 1) provide approximately 1600 to 2100 calories.

TABLE 1
Food values of commonly used diabetic diets

Carbohydrates	Proteins	Fat	Calories
150	80	80	1640
180	80	80	1800
150	100	60	1540
200	100	100	2100

Compare these with the recommended calorie allowances of the National Research Council in the 1953 revision. (See Table 2A and B). It is apparent that the diabetic diets are inadequate in calories for most adults except middle-aged and elderly females. The prime requisite of the body is for calories. The administration of large excesses of vitamins will not prevent starvation if the caloric intake is inadequate.

In the case of the growing children, the diabetic diets are even less adequate. An analysis of the diabetic diets as prescribed fails to show any over 2600 calories and few of them even at the 2400-calorie level. The National Research Council suggested allowances as shown in Table 2A and B reach a much higher level. The calorie content of a diet should supply the needs of fully healthy individuals for their age, sex, size and activity to maintain optimum body weight, *support the optimum rate of growth* and full physical activities.

Protein allowances for the diabetic should be even greater than for the nondiabetic. The standard allowance of 1 gm. per kg. of body weight for adults is acceptable for the healthy individual. During periods of active growth the protein needs rise to 3 gm. per kg. of body weight, and during periods of slow growth go down to 1.5 gm. per kg. of body weight. These protein recommendations are predicated upon the consumption of an adequate caloric intake. The diabetic, it has been demonstrated, develops a negative nitrogen balance during episodes of ketosis, even very mild, transient ones. In deep ketotic acidosis, hourly nitrogen losses equivalent to 100 gm. of protein have been measured. This means that the diabetic must be insured with liberal amounts of protein

TABLE 2A
Daily dietary allowances[1] (revised 1953) designed for the maintenance of good nutrition of healthy persons in the U.S. as recommended by the Food and Nutrition Board, National Research Council

	Allowances Are Considered to Apply to Persons Normally Vigorous and Living in Temperate Climate						
	Age Years	Weight kg. (lb.)	Height cm. (in.)	Calories	Protein gm.	Calcium gm.	Iron mg.
Men	25	65 (143)	170 (67)	3200[2]	65	0.8	12
	45	65 (143)	170 (67)	2900	65	0.8	12
	65	65 (143)	170 (67)	2600	65	0.8	12
Women	25	55 (121)	157 (62)	2300[2]	55	0.8	12
	45	55 (121)	157 (62)	2100	55	0.8	12
	65	55 (121)	157 (62)	1800	55	0.8	12
	Pregnant (3rd Trimester)			400	80	1.5	15
	Lactating (850 ml. daily)			1000	100	2.0	15
Infants[3]	1/12-3/12	6 (13)	60 (24)	kgx120	kgx3.5	0.6	6
	4/12-9/12	9 (20)	70 (28)	kgx110	kgx3.5	0.8	6
	10/12-1	10 (22)	75 (30)	kgx100	kgx3.5	1.0	6
Children	1-3	12 (27)	87 (34)	1200	40	1.0	7
	4-6	18 (40)	109 (43)	1600	50	1.0	8
	7-9	27 (59)	129 (51)	2000	60	1.0	10
Boys	10-12	35 (78)	144 (57)	2500	70	1.2	12
	13-15	49 (108)	163 (64)	3200	85	1.4	15
	16-20	63 (139)	175 (69)	3800	100	1.4	15
Girls	10-12	36 (79)	144 (57)	2300	70	1.2	12
	13-15	49 (108)	160 (63)	2500	80	1.3	15
	16-20	54 (120)	162 (64)	2400	75	1.3	15

[1]In planning practical dietaries, the recommended allowances can be attained with a variety of common foods also providing other nutrient requirements less well known; the allowance levels are considered to cover individual variations among normal persons as they live in the United States subjected to ordinary environmental stresses common thereto. Other nutrients discussed in the report of the Board include: Fat, Water, Sodium Chloride, Phosphorus, Copper, B_6, Vitamin B_{12}, Folacin, Biotin, Pantothenic Acid, Vitamin K, and Fluoride.

[2]These calorie recommendations apply to a moderate degree of activity for the standard man (40-hour work week with at least 8 hours of weekend outside physical activity, in temperate climate). For the urban "white-collar" worker they are probably excessive. In any case, the calorie allowance must be adjusted to the actual needs of the individual as required to achieve and maintain his desirable weight.

[3]The recommendations for infants pertain to nutrients derived primarily from cow's milk or commercial milk preparations. There should be no question that human milk is a desirable source of nutrients for infants, although expected intakes may not provide the above recommended levels of certain nutrients; e.g., protein, calcium, riboflavin and thiamine.

This table has been made available by special permission in advance of publication of the full text of the Board's report. This will be published in the spring of 1954 as a bulletin in the numbered series issued by the National Academy of Sciences.

TABLE 2B

Daily dietary allowances (revised 1953) designed for the maintenance of good nutrition of healthy persons in the U.S. as recommended by the Food and Nutrition Board, National Research Council

	Allowances Are Considered to Apply to Persons Normally Vigorous and Living in Temperate Climate						
	Age Years	Vitamin A I.U.	Thiamine mg.	Riboflavin mg.	Niacin mg.	Ascorbic Acid mg.	Vitamin D I.U.
Men	25	5000	1.6	1.6	16	75	
	45	5000	1.4	1.6	14	75	
	65	5000	1.2	1.6	12	75	
Women	25	5000	1.2	1.4	12	70	
	45	5000	1.0	1.4	10	70	
	65	5000	1.0	1.4	10	70	
	Pregnant	6000	1.5	2.0	15	100	400
	Lactating	8000	1.5	2.5	15	150	400
Infants[3]	1/12-3/12	1500	0.4	0.5	4	30	400
	4/12-9/12	1500	0.5	0.8	5	30	400
	10/12-1	1500	0.5	0.9	5	30	400
Children	1-3	2000	0.6	1.0	6	35	400
	4-6	2500	0.8	1.2	8	50	400
	7-9	3500	1.0	1.5	10	60	400
Boys	10-12	4500	1.3	1.8	13	75	400
	13-15	5000	1.6	2.1	16	90	400
	16-20	5000	1.9	2.5	19	100	400
Girls	10-12	4500	1.2	1.8	12	75	400
	13-15	5000	1.3	2.0	13	80	400
	16-20	5000	1.2	1.9	12	80	400

See footnotes of Table 2A.

at all times. After ketotic episodes, a distinct effort should be made to replenish the losses as rapidly as possible. The nature of the amino acid requirements to replenish these protein losses are unknown. In accordance with the law of the minimum, no amino acid mixture is more efficient than the least amount of the essential amino acid present. It is necessary, therefore, to supply an excess of mixed proteins in order to insure the adequacy of the amino acid mixture. The protein allowance of the diabetic adult should be in the order of 100 gm. each day and for children and adolescents, proportionately as high. It must be remembered that there is a real possibility that many of the degenerative diseases seen in the accelerated form in the diabetic can be nutritional in origin.

The diabetic should be encouraged to consume a diet which is nutritionally adequate. Sufficient insulin should be given to enable him to metabolize the ingested nutrients.

HERBERT POLLACK, M.D.
Associate Physician for Metabolic Diseases
The Mount Sinai Hospital, New York, N. Y.

Publicity Regarding Medical Science in Spanish America

The Interlingua Division of Science Service has announced the publication of a booklet containing abstracts from "The Story of the Adaptation Syndrome," By Dr. Hans Selye, translated into Spanish. This illustrates one phase of the work of Science Service, "the Institution for the Popularization of Science," which was organized in 1921 as a non-profit corporation with trustees nominated by the National Academy of Sciences, the National Research Council, the American Association for the Advancement of Science, the E. W. Scripps Estate and the Journalistic Profession.

The Interlingua Division, through this Spanish publication, will make possible dissemination in Latin America of the interesting and important concept pioneered by Selye, which has received such wide attention from the medical profession of this Continent. The booklet contains a glossary of the abbreviations and technical terms which have been used in writings on stress. It presents with illustrations the ideas concerning stress proposed in 1936 and also developments which have appeared in 1937, 1944, 1945 and 1952. It gives an excellent review of the subject for readers in Spanish-speaking countries.

BOOK REVIEWS

LONG-TERM DIABETES: *The Clinical Picture in Diabetes Mellitus of 15-25 Years' Duration with a Follow-up of a Regional Series of Cases. By Knud Lundbaek, M.D., Lecturer in Internal Medicine, Ophthalmological Section in collaboration with Viggo A. Jensen, M.D., Professor of Ophthalmology, Aarhus University Medical School, Copenhagen, Denmark. $4.80, Pp. 197, with 3 general tables. Ejnar Munksgaard, Copenhagen, and Lange, Maxwell & Springer, Ltd., London, New York, 1953.*

In this monograph the senior author has collected and analyzed data regarding 234 patients (104 male and 130 female) with diabetes of 15 to 25 years' duration at the time of follow-up or at death. Only those with onset of diabetes between 1924 and 1935 were included. All resided, or had resided, in the municipality of Aarhus, Denmark (population about 115,000) in the course of the period 1924-1950. At the time of study, 165 or 70 per cent of the 234 patients were living; fourteen of the males and 18 of the females were under the age of 40. There were 59 patients with onset of diabetes at the age of 25 years or under. It was estimated that from one-fourth to one-fifth of the diagnosed diabetics of Aarhus were long-term in the sense used in the monograph.

Detailed studies and tabulations were made of the case records of all patients, dead and living, who had had hospital admissions. Living patients were recalled and carefully questioned and examined. An attempt was made to form an estimate as to how much care the individual patient had shown in treatment and control of diabetes over the years. The examination included careful ophthalmologic study, electrocardiography, determination of the capillary resistance, hemoglobin, sedimentation rate, serum protein, serum cholesterol and sugar, ketone and protein content of urine. Finally, an attempt was made to correlate the degree of control of diabetes with the presence or extent of complications. Of the 165 living diabetics, it was estimated that 95 had been poorly controlled and 48 well controlled. In 22 cases it was impossible to speak with certainty regarding the degree of control. Thus, among the patients in whom an estimate could be made, the poorly controlled were 66 per cent.

About nine-tenths of the patients presented various combinations of abnormalities in the eyes, kidneys, heart and legs. Retinopathy, present in about 80 per cent of the patients, was most common. Signs of renal disease occurred in about one-fourth of the living and about one-half of the deceased patients. Heart disease and vascular abnormalities of the legs were of frequent occurrence among the elderly patients. "Neuropathic syndrome of the feet" was for some reason or other not common and not observed with greater frequency in the elderly than in the younger patients. Arterial hypertension (blood pressure readings over 150/100) and hypercholesterolemia showed a high incidence. Increased capillary fragility was observed in about one-third of the patients while abnormally decreased serum protein values were found in about one-tenth. In about one-tenth no abnormalities of the kidneys, heart, eyes or legs were found but a number of these had other defects, including arterial hypertension, high serum cholesterol values, and increased capillary fragility.

The author points out that there is all too commonly a tendency to view with great pessimism the situation in long-term diabetes. He emphasizes that it is as important to note among his patients that only 2 per cent of the living were blind as it is to observe that diabetic retinopathy of some degree or other could be demonstrated in 80 per cent.

Lundbaek regards the various long-term diabetic manifestations as different expressions of generalized long-term diabetic vascular disease. He states that this is dependent on the duration of the diabetes, that it develops slowly over a number of years and can be recognized only when diabetes has been present for 8, 12 or more years. Among elderly patients who apparently disprove the concept of the relation of vascular disease to duration of diabetes, close questioning will almost always afford evidence that the disease is of longer standing than supposed and that certain mild symptoms of diabetes will have been present for many years. He quotes the current thought that the abnormal material deposited in the thick-walled retinal aneurysms and the nodular lesions of intercapillary glomerulosclerosis may consist of polysaccharides or polysaccharide-containing conjugated proteins. The long-term diabetic vascular disease occurs in small and large arteries, veins and capillaries.

When information regarding the degree of control of diabetes over the years was correlated with the presence and extent of vascular disease it was found that the "vascular syndrome of the feet" occurred about as commonly in the group as in the other. However, retinopathy, renal disease, heart disease, abnormal capillary

fragility and vascular calcification were more common in patients with poor control than in those with good control. In the case of retinopathy, renal disease and calcification of leg arteries, the differences between percentages of incidence were considerable and, in fact, quite impressive but the author states that calculation showed that in a statistical sense the differences were significant only in the case of retinopathy. Among the patients with good control, 33 per cent showed no retinopathy whereas only 15 per cent of those with poor control were free from this complication.

Lundbaek believes that although it is difficult to show beyond doubt that late complications are correlated with degree of control of diabetes, from a practical point of view such a conclusion is justifiable if not imperative. "This conclusion cannot be regarded as bad tidings to the diabetics, imposing intolerable restrictions and privations. On the contrary—the conclusion is that it pays to be careful. The happy-go-lucky way of life is to be discouraged, but a happy life is by no means excluded by attention to reasonable advice and treatment."

CARDIOVASCULAR-RENAL DISEASE IN DIABETES MELLITUS. *A Clinical Study. By Sverre Aarseth, M.D., Oslo City Hospital, Oslo, Norway. Pp. 252. Bohler and Larsen, Oslo, 1953*

This interesting study, based on observations of 312 diabetic patients with 382 admissions to the Oslo City Hospital in the period of October 1, 1948, to March 1, 1951, is worthy of reading by those particularly interested in diabetes mellitus. Details of the patient are given in reference to sex, age, duration of diabetes, heredity, complicating diseases, treatment and insulin requirement. The correlation between diabetes and obesity and between diabetes and diseases of the endocrine organs are discussed. Particular attention is given to the subject of diabetic retinopathy, the occurrence of hypertension, diseases of the heart, incidence and manifestations of arteriosclerosis, occurrence of renal disease and diabetic neuropathy. An extensive review of the literature on the various subjects is made, and the bibliography includes several hundred references.

The incidence of cardiovascular and renal diseases was found to be higher than that in the nondiabetic population, as might have been expected. The only weakness in the study lies in the fact that the patients were all hospitalized patients who had severe enough complications to be followed in the institution. It was noted that most of the complications studied were in the older age group. A fairer picture of the complications of diabetes mellitus would take into consideration long-time observation on the many patients who remain out of the hospital, while they are coming to doctors' offices and clinics for treatment. Nevertheless, the study has been very well conducted.

The number of diabetics in Norway was estimated in 1948 to be between 10,000 and 15,000 persons. Eighty of the patients of the 312 in the study died during the period of study. Of these, autopsy was performed on 49.

Diabetic retinopathy was found in 42 per cent of those examined for this condition. It was highest in the group with the greatest insulin requirement and the greatest incidence of coma. There was a great correlation between retinopathy and the duration of the diabetes. No relationship was noted between the retinopathy and vascular or renal disease. Hypertension, that is, a blood pressure of 160/90 on repeated readings, occurred only in patients over 40 years old, with one exception. Ninety-five per cent were over 50 years of age. After this age there were nearly twice as many females as males with hypetension, 61 per cent of the females and 34 percent of the males. There was correlation between obesity and hypertension among the females but not among the males, with concurrence of hypertension and considerable obesity being five times as frequent among the females as among the males.

Reduced renal function was found mainly among the hypertensives. Permanent proteinuria was present in 40 per cent of the hypertensive females and in 48 per cent of the hypertensive males, but in only one patient with a normal blood pressure. Myocardial infarction was a frequent occurrence in the group (12 per cent). The male to female ratio was 1.33:1, whereas in the total hospital population the ratio was 2.5:1. Myocardial infarction in the diabetics occurred in the same age groups as in nondiabetics. Calcific disease of the aortic valve was found almost twice as frequently in the diabetics as in the total population of the hospital. Diseases of the heart was the cause of death of nearly half of the number of the diabetics who died. Roentgenologic demonstration of arteriosclerosis in the lower extremities or the pelvic arteries was made in 55 per cent of those examined and was equally frequent in males and females. Calcification of the peripheral arteries was found mainly in the patients over 40 years of age, but in the juvenile diabetics, duration of the diabetes seemed to be the dominant factor in the development of peripheral arteriosclerosis. However, in this series there were very few patients under 30 years of age.

Permanent proteinuria was found in 25 per cent of

the total material and equally distributed between the two sexes. The frequency increased considerably with age. Infections in the urinary tract were common, and pyelonephritis was the renal disease of greatest clinical importance. Pyelonephritis with papillary necrosis occurred in three cases. Arteriosclerosis of the small and medium renal arteries was frequent and often pronounced. Intercapillary glomerulosclerosis was found in 14 per cent, but may not have represented the only renal lesion. Renal disease was the sole or contributory cause of death in 17.5 per cent of fatal cases.

THE ACTION OF INSULIN. *By Niels Haugaard, Ph.D., Assistant Professor of Physiological Chemistry in Research Medicine, School of Medicine, University of Pennsylvania, Philadelphia, and Julian B. Marsh, M.D., Assistant Professor of Physiological Chemistry, Graduate School of Medicine, University of Pennsylvania, Philadelphia, $3.75. Pp. 113, illustrated. Charles C. Thomas, Springfield, Ill., 1953.*

The authors of this monograph and Dr. W. C. Stadie, who introduces the subject, are well known for their studies of the effects of insulin on carbohydrate metabolism of the rat diaphragm *in vitro* and of modifications in insulin action induced by anterior pituitary and adrenal cortical hormones on such preparations. This subject, as might be expected, is dealt with more fully than some others. It is stated in the preface that the work was not conceived as a comprehensive review of the actions of insulin.

The aim of the monograph is to present the results of recent investigations that shed some light on the problem of the mechanism of insulin action. In preliminary chapters an attempt has been made to set subsequent experimental results and theories in their proper perspectives by outlining the essentials of intermediary metabolism, the physiology of insulin action, and diabetic metabolism. The reviewer feels that despite this introductory development, the fundamental significance of some experiments will remain obscure to many not intimately associated with this field of study. The concepts of the problem would have been clarified for the readers, if the authors had made a greater attempt in the discussions to integrate the meanings of experimental data presented.

Discussion of the chemistry of insulin, experimental diabetes, and some clinical aspects of insulin action are also included in the text.

The monograph is provided with an adequate index, and tables and graphs that are informative and easily understood. It is well documented, with excellent references listed at the end of each chapter. The book should achieve its purpose of interesting both the clinician and the research worker, and belongs on the shelves of diabetic specialists, many medical internists and, of course, all medical librarians. It provides an excellent outline for the clinician who desires a more fundamental insight into some problems that face him in practice, and a review that will do much to maintain the insulin investigator's knowledge of contemporary work and thought.

Trends and Needs in Nutrition

In the history of nutrition science, one major trend is outstanding: The application has become ever broader. Prior to World War I, available knowledge was used mainly for the prevention or alleviation of dietary deficiency diseases in the individual and small groups. Scurvy, rickets and goiter were effectively countered at that level.

The next step, an organized public health approach, was planned distribution of preventive foods, such as butter, iodized salt and cod liver oil. Meanwhile, the isolation of vitamins progressed; and just prior to World War II, it became practical to improve staple foods with synthetic nutrients as a means of attacking deficiency diseases in large populations. Vitamin D was added to milk, vitamin A to margarine; and in 1941 the same broad approach was applied to the prevention of beriberi, pellagra, ariboflavinosis, and iron-deficiency anemia, when white flour and bread were first enriched with thiamine, niacin, riboflavin and iron.

Nationwide control of specific dietary diseases was now feasible, and a program to that end was soon launched. This program included improvements in agricultural practices, better nutrition education, a national school lunch program, and advances in food handling, preservation and distribution.

This trend in the nutrition movement—broadening of the attack—is reflected in accelerated progress against many nutritional disorders.

From *Trends and Needs in Nutrition,* by W. H. Sebrell, Jr., M.D., in The Journal of the American Medical Association, May 2, 1953

Otto Folin

Benefactor of Diabetics through Biochemistry

Alexander Marble, M.D., Boston, Mass.

To students, laboratory workers, teachers and practitioners of medicine the world over, the name of Folin is well known. In laboratories everywhere, one or more of his methods of analysis of urine, blood and other body fluids is in daily use. Untold patients, including those with diabetes, have benefited from Folin's development of simple and accurate biochemical methods applicable to small quantities of material. Moreover, the debt and the gratitude of both patient and physician do not end with acknowledgement of his development of laboratory technics. Apart from these, he contributed much to the total of knowledge regarding the intermediary metabolism of protein and carbohydrate. Early in his scientific career he became interested in the processes by which complex food materials are absorbed and utilized within the body.

Otto Knut Olof Folin was born on April 4, 1867 in the village of Asheda in southern Sweden. His father, Nils, was a tanner. His mother, Eva, was a woman of ability and courage who was highly regarded throughout the large district which she served as the official midwife. At the age of fifteen, Otto joined the wave of Swedish immigration to America and came to Stillwater, Minnesota, a lumber town, to live with his older brother, Axel, who had earlier taken land there. After graduation from the local schools he went to the University of Minnesota, where he supported himself. After receiving a B.S. degree in 1892, he entered the University of Chicago which had opened only the year before.

As a graduate student in organic chemistry at the University of Chicago, Folin came under the guidance of Stieglitz, the outstanding chemist. Folin's doctoral thesis, a dissertation "On Urethanes," was completed and published in 1896 although he did not receive his Ph.D. degree until 1898. Having decided upon a career in physiological chemistry, early in 1897 he went to Europe for study. He began with Olof Hammarsten in Upsala where he carried out studies with glycoprotein from the submaxillary gland. Later he worked with Salkowski in Berlin and with Kossel in Marburg. At Marburg began his life-long interest in the intermediate stages of protein metabolism. As the result of his European stay, several papers were published in Hoppe-Seyler's Zeitschrift.

At this time, just at the turn of the century there were only a few schools which had a department of physiological chemistry and so when Folin returned to the United States in 1898 he found no opening. He worked for a year as an industrial chemist in Chicago before being appointed in the fall of 1899 as Assistant Professor of Analytical Chemistry at the University of West Virginia. In September of that year, he married Laura Churchill Grant of St. Paul, a Vassar graduate. Although Folin remained at West Virginia only one year, he gave a course in physiological chemistry which so aroused the interest of his students that certain of them, including the later renowned Philip A. Shaffer, decided to devote their lives to work in this field.

At this time there was an attempt to connect psychiatry with the exact sciences, especially chemistry, and so in 1900 Folin received an appointment at McLean Hospital for mental disease in Waverley, Mass. (now a neuro-psychiatric unit of the Massachusetts General Hospital) to work on this problem. The laboratory which he established there, solely for biochemical research, was the first of that sort in any hospital in the United States.

Folin's first object was to determine accurately the quantities of the main constituents of the urine as an index and measure of the chemical reactions within the body. Most of the urinary constituents were then known qualitatively, but methods for their determination were in many cases so laborious or complicated that no approximately complete analysis of a single urine specimen had been accomplished and complete consecutive daily analyses during a metabolism experiment were impossible. He, therefore, undertook the task of

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simplifying procedures for the quantitative analysis of urine.

Among the methods Folin devised was a colorimetric procedure for creatinine and creatine, notable not only because it is still the standard technic for these substances but also because it introduced the colorimeter into biochemistry and demonstrated the practical value of color comparisons as the basis for analysis of small amounts of material. From Folin while at the McLean laboratory came a series of papers describing not only these analytical methods but also those for sulfur and sulfates, uric acid, urea and ammonia. The development of new and simpler methods led to his classic work on the composition of the urine and to his theory of protein metabolism. Folin maintained, contrary to views commonly held at that time, that food protein after digestion was absorbed directly into the blood as small amino-acid fragments and not in the form of protein resynthesized during absorption. He made a clear distinction between the components of the urine that were independent of the amount of ingested protein and those that depended on it. In this manner he arrived at his distinction between endogenous and exogenous protein metabolism.

Folin's work at the McLean Hospital served to call attention to his outstanding ability as a biochemist and led to his appointment in 1907 as Associate Professor and in 1909 as Hamilton Kuhn Professor of Biological Chemistry at Harvard Medical School. During the first few years at his new post he prepared material for his lectures to students and his "Laboratory Manual," which was so widely used that it ran into five editions. He continued his interest in the products of the digestion of food protein and sought to identify them in the blood and tissues. As with his earlier studies of urine, he found it necessary first to develop simple, rapid and accurate methods requiring only small quantities of material. One difficulty was, of course, the fact that he was attempting to determine tiny amounts of nitrogenous substances which occur naturally along with the abundant protein of blood and tissues. With Denis, he worked out a method in which proteins and colloidal material are precipitated without heat, the filtrate submitted to a micro-Kjeldahl digestion and the ammonia formed determined colorimetrically by use of Nessler's reagent. For the clinician, this provided a relatively easy way of determining the "non-protein nitrogen" of the blood. At about the same time Folin introduced practical methods of chemical analysis for other constituents of the blood such as creatinine, urea, uric acid and sugar.

In 1912, there appeared an article on phosphotungstic and phosphomolybdic acid compounds as color reagents. The continuation of this work occupied much of Folin's time during the rest of his life. He based upon it his methods for determinations of phenol, uric acid and blood sugar, non-specific reductions resulting from the formation of wholly unknown and double salts obtainable with difficulty. It took all of Folin's unusual experience and technical skill to establish the conditions that finally made the methods practically specific. His last paper in the August 1934 number of the *Journal of Biological Chemistry* was concerned with the preparation of the uric acid reagent.

In 1919, Folin and Hsien Wu brought out an historical paper in the *Journal of Biological Chemistry* entiled "A System of Blood Analysis." An important feature was the preliminary precipitation of blood with tungstic acid, a procedure without heating and without excess acid present at any step of precipitation, yielding a practically neutral filtrate. The filtrate may be used to determine sugar, non-protein nitrogen, urea nitrogen, uric acid, creatinine and even amino-acid nitrogen and chloride.

Shortly after Professor Folin's death there was found in his desk at the Harvard Medical School a two-page manuscript written and signed by him and dated April 9, 1924. It gives his own estimate of the value of various phases of his work. It reads as follows:

"When I was appointed chemist to the McLean Hospital in 1900, it became my duty to do chemical research on problems bearing on mental diseases. As the pathologist wanted all the brain material I took to the field of metabolism.

"It was hopeless to try to find deviations from the normal in the metabolism of the insane without far more exact knowledge of the human waste products than was available. My immediate and comprehensive problem became, therefore, the chemistry of urine. I realized that by thus interpreting my duty to the hospital, I could do work of more general interest. I probably also followed my taste, for I enjoyed the mere puzzle aspect which is always present when one tries to devise a new method.

"My papers on the 'Laws Governing the Chemical Composition of Urine' and a 'Theory of Protein Metabolism' (1904) will probably be considered my best; but the data for those papers came easily and naturally by the help of the new methods for the determination of urea, ammonia and creatinine which I had devised during the preceeding three years.

"My later studies—'Protein Metabolism from the

Standpoint of Blood and Tissue Analysis'—in the main represent attempts to pursue experimentally theoretical concepts which I had developed on the basis of urine analysis. My elucidation of amino acid absorption does not stand out well, partly because it was presented in the form of a series of short papers and partly because Van Slyke soon came into the field with a method of his own. My 'best work' in the field of blood and tissue analysis, aside from the methods developed, should be the work of uric acid, now in press. It will be the starting point for much new metabolism literature."

His "best work" from the viewpoint of most readers of DIABETES was probably the Folin-Wu method of blood sugar determination. For several decades, it has been widely used in the clinical laboratories of this country. Although other methods, particularly those for the determination of "true glucose" in the blood now are becoming more popular, the Folin-Wu test has been the means of accurate diagnosis of diabetes and guidance of the treatment of countless patients.

Folin's interests were in his family, his laboratory and the game of golf which he played well. He was quiet, modest and unassuming. Tall, erect, and spare, he appeared at first sight somewhat grim because of a left facial paralysis (incurred during surgical removal of a parotid tumor in 1905) but this soon became unnoticed by associates and students. His quaint and kindly humor and his friendly manner made him well-liked. However, his students will recall that he did not hesitate to criticize the views of those with whom he did not agree. Above all, his manner and methods both in teaching and research were simple and direct. Students at Harvard Medical School were extraordinarily fond of him. There was no spoonfeeding of students and very little close direction of effort, either of medical students or graduate students, but instead there was the supreme example and inspiration of accurate work and accomplishment.

When the *Journal of Biological Chemistry* was established in 1905, Folin was already an investigator of note. He was a member of its first group of collaborators. In 1920, when the Journal became the publication of the American Society of Biological Chemists, he was appointed chairman of the Editorial Committee and thereafter remained an active and influential member of the committee.

Among the honors bestowed upon Professor Folin were membership in the National Academy of Sciences, honorary membership in the Medical Society of Sweden, honorary degree of D.Sc. by Washington University (1915) and the University of Chicago (1916), honorary M.D. by the University of Lund (1918), and the Scheele Medal of the Stockholm Chemical Society (1930). The list of his publications as compiled by Professor Harry C. Trimble for a volume now in the Harvard Medical School Library contains 171 items with dates ranging from 1897 to 1934.

In the fall of 1934, Professor Folin was to have been honored at a dinner at which his portrait by E. Pollak-Ottendorff was to have been presented to the University. However, on October 25, 1934, at the age of 67 he died at the Peter Bent Brigham Hospital the day following a surgical procedure carried out as a sequel to a prostatectomy some three years before. He was buried in New Hampshire at the foot of Mt. Kearsarge not far from the cottage where he loved to spend his summers.

The portrait of Professor Folin from which the picture on the front cover of this issue of DIABETES was made, now hangs in the Bowditch Library of Harvard Medical School very near the laboratories in which he worked for so many years. One notes the colorimeter with a volumetric flask on each side. In the original painting, the liquid in the flask on the left was colored orange and that on the right blue. The arrangement, Folin's own idea, was to show two reactions of much importance in his life as a biochemist, the orange color of the creatinine determination and the blue color of the uric acid procedure.

ACKNOWLEDGEMENTS

The writer was fortunate in having available in the library of Harvard Medical School a collection of Folin's books and reprints and a memorial volume containing articles and letters written regarding him following his death. Grateful acknowledgement is hereby made for material which has been taken freely from these sources. Thanks are expressed also to Professor Trimble for information, suggestions and advice. Published articles which were consulted include those listed in the references.

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Organization Section

Second Postgraduate Course in Diabetes and Basic Metabolic Problems Rochester, Minnesota, January 18-20, 1954

Lectures and discussions on the clinical aspects of diabetes, and its complications will be featured at the Second Postgraduate Course in Diabetes and Basic Metabolic Problems.

This Course will be offered by the American Diabetes Association under the direction of Edward H. Rynearson, M.D., and Randall G. Sprague, M.D., Consulting Physicians, Section of Medicine, Mayo Clinic, and Professors of Medicine, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

It will be conducted on January 18, 19 and 20, 1954, at the Mayo Clinic and Mayo Foundation in Rochester. The scientific sessions will be held in Frank C. Mann Hall, Medical Sciences Building. Open to all members of the medical profession, the Course has been developed by the Association's Committee on Professional Education, of which Edward L. Bortz, M.D., is chairman.

The maximum number of registrants which can be accepted is 125. The fee is $40 for members of the Association and $75 for non-members. This must be paid to the American Diabetes Association, 11 West 42nd Street, New York City, at the time of filing application for the course. Information as to hotel accommodations in Rochester will be sent to registrants with their matriculation card confirming acceptance for the Course.

The Program is as follows:

Monday morning, January 18.

CLINICAL ASPECTS OF DIABETES

Presiding: Charles H. Best, M.D., Director and Professor in the Banting and Best Department of Medical Research, Professor of Physiology, University of Toronto.

Differential Diagnosis of the Meliturias, Alexander Marble, M.D., Clinical Associate in Medicine, Harvard Medical School; Physician, New England Deaconess Hospital and Joslin Clinic, Boston.

Selective Treatment of Diabetes According to Severity, Arthur R. Colwell, M.D., Professor of Medicine, and Chairman, Department of Medicine, Northwestern University Medical School, Chicago.

Management of Labile or Brittle Diabetes, Henry B. Mulholland, M.D., Assistant Dean and Professor of Internal Medicine, University of Virginia Medical School, Charlottesville Va.

Clinical Management of Diabetes in Infancy and Childhood, Robert L. Jackson, M.D., Professor of Pediatrics, State University of Iowa, College of Medicine, Iowa City.

The Curability of Diabetes, Frank N. Allan, M.D., Executive Director, Medical Department, Lahey Clinic, Boston.

Discussion by participants in morning session, Doctor Colwell, Chairman.

The afternoon program:

Presiding: Doctor Bortz, Associate Professor of Medicine, University of Pennsylvania School of Medicine, Philadelphia.

About the Pancreas, Doctor Best.

The Clinical Use of Various Types of Insulin, Doctor Colwell.

Experiences with NPH Insulin in Childhood Diabetes, A. L. Chute, M.D., Professor of Pediatrics, University of Toronto; Chief of Pediatrics, Hospital for Sick Children, Toronto; and Professor, Banting and Best Department of Medical Research.

Present Status of New Insulin-Zinc Modifications, Franklin B. Peck, Sr., M.D., Director, Medical Research Co-operation, The Lilly Research Laboratories, Indianapolis; Associate Professor of Medicine, Indiana University School of Medicine, and Consultant, Indianapolis General Hospital.

Complications of Insulin Therapy, Doctor Mulholland.

Errors in Treatment, Henry T. Ricketts, M.D., Professor of Medicine, The School of Medicine, University of Chicago.

Discussion by participants in afternoon session, Doctor Best, Chairman.

Evening, social hour, dinner, Rochester Country Club.

The program: *A Practical and Metaphysical Demonstration of Visual Acuity Versus Manual Dexterity,* Oliver H. Beahrs, M.D., Ph.D. in Prestidigitation.

Tuesday morning, January 19.

COMPLICATIONS OF DIABETES

Presiding: Doctor Colwell.

Etiology and Principles of Treatment of Diabetic Acidosis, Herbert Pollack, M.D., Lecturer in Medicine, College of Physicians and Surgeons; Associate Physician for Metabolic Diseases, The Mount Sinai Hospital, N. Y.

Electrolyte Metabolism in Diabetic Acidosis, Doctor Sprague.

Rapid Bedside Micromethods for Estimating Sugar and Ketones in Blood; Clinical Applications, George M. Guest, M.D., Professor of Research Pediatrics, University of Cincinnati College of Medicine.

Some Aspects of the Pathology of Diabetes, Warren A. Bennett, M.D., Consulting Physician, Section of Pathologic Anatomy, Mayo Clinic; Assistant Professor of Pathology, Mayo Foundation, Graduate School, University of Minnesota, Rochester.

Current Concepts of the Pathogenesis of the Degenerative Complications of Diabetes, Doctor Ricketts.

Diabetic Nephropathy, Doctor Marble.

Discussion by participants in morning session, Doctor Marble, Chairman.

The afternoon program:

Presiding: Doctor Allan.

Lesions of the Feet, Frederick W. Williams, M.D., Associate Clinical Professor of Medicine, New York Medical College, New York City.

The Course of Diabetic Retinopathy, Thomas P. Kearns, M.D., and Henry P. Wagener, M.D., Consulting Physicians, Section of Ophthalmology, Mayo Clinic.

Neurological Complications of Diabetes, Allan A. Bailey, M.D., Consulting Physician, Section of Neurology, Mayo Clinic; Assistant Professor of Neurology and Psychiatry, Mayo Foundation.

Pregnancy in Diabetes, M. David Allweiss, M.D., Associate in Medicine, Northwestern University Medical School; Associate Attending Physician in Medicine, Michael Reese Hospital, Chicago.

Prediabetes in Pregnancy, Joseph Hoet, M.D., Professor and Head of Medicine, University of Louvain, Louvain, Belgium.

Discussion by participants in afternoon session, Doctor Williams, Chairman.

Tour of Medical Sciences Building or Mayo Clinic New Building.

Wednesday morning, January 20.

NUTRITIONAL REQUIREMENTS AND DIET IN DIABETES

Presiding: E. Perry McCullagh, M.D., Head, Section of Endocrinology and Metabolism, Cleveland Clinic, Cleveland.

The Significance of Food Analyses, William H. Olmsted, M.D., Associate Professor of Clinical Medicine (Emeritus), Washington University School of Medicine; Staff of Barnes Hospital and St. Marys Hospital, St. Louis.

Dietary and Nutritional Requirements, Doctor Pollack.

Nutritional Requirements in Childhood Diabetes, Doctor Jackson.

Diabetes Mellitus and Obesity, Thomas P. Sharkey, M.D., Consultant in Metabolic Diseases, Miami Valley Hospital, Dayton; Assistant Professor of Clinical Medicine, College of Medicine, Ohio State University, Columbus. (Paper to be presented by John H. Warvel, M.D., Indianapolis.)

Teaching the Patient the Diet, Doctor Olmsted.

Discussion by participants in morning session, Doctor Olmsted, Chairman.

The afternon program:

SPECIAL TOPICS

Presiding: Doctor Sprague.

Hyperinsulinism and Insulin Malingering, Doctor Rynearson.

The Hyperglycemic Glycogenolytic Factor of the Pancreas, Gerald A. Wrenshall, Ph.D., Associate Professor, Banting and Best Department of Medical Research.

Some Emotional Aspects in the Management of Patients with Diabetes Mellitus, Howard P. Rome, M.D., Consulting Physician, Section of Psychiatry, Mayo Clinic; Professor of Psychiatry, Mayo Foundation.

Diabetes Associated with Hyperfunctioning Lesions of the Pituitary and Adrenal Cortex, Doctor McCullagh.

Hemochromatosis, Maurice H. Stauffer, M.D., Consulting Physician, Section of Medicine, Mayo Clinic; Instructor in Medicine, Mayo Foundation.

Tour of Mayo Clinic New Building or Medical Sciences Building.

Winner of the 1953 Award for the Best Paper by Medical Students and Interns

The Editorial Board of DIABETES takes great pleasure in announcing the selection of Alan William Feld, New York City, as winner of the 1953 contest for the best paper on diabetes by medical students and interns. A number of papers were reviewed by the Board and Mr. Feld's, on "The Endocrinology of the Pancreas," was chosen as the outstanding contribution.

Now a third-year student in the College of Physicians and Surgeons of Columbia University, Mr. Feld graduated from Princeton in 1951 summa cum laude with a Bachelor of Arts degree. In his Junior year he was elected to Phi Beta Kappa. Scholastic achievements are not limited to his college work, as he was Valedictorian of his high school class and received the Bausch and Lomb Science Medal. While in high school he took an active interest in debating, oratory, journalism and student government. He won the New Jersey State Debating Championship, as well as the city, county and state regional American Legion Oratorical Contest championships. Also, he served as editor of his high school paper which won honorable mention in *Scholastic Magazine's* National Literary Contest. As a Princeton undergraduate he was on the Editorial Board of the *Princeton Tiger* and was one of the organizers and a member of the Board of Governors of the Pre-Medical Society. Along with scholastic achievements he has found time to pursue an interest in antiques and the theater.

Alan William Feld, winner of the 1953 contest for the best paper on diabetes

As announced in previous issues of the Journal, the award of $250 was made possible through the generosity of the St. Louis Diabetes Association.

In addition to Mr. Feld's contribution there were many other excellent papers submitted which the Editorial Board felt should receive recognition. Although not previously announced, it was decided that honorable mention should be given to five additional authors. A one-year free subscription to DIABETES, beginning with the January-February (Vol. 3, No. 1) 1954 issue, will be sent to those listed below.

Windsor Howard Dalrymple, M.D., Philadelphia, submitted a paper on "Insulin Resistance and Hypothalamic Injury: Report of a Case." Doctor Dalrymple received a Bachelor of Science degree in Mechanical Engineering in 1949 from Cornell University after transferring from Rensselaer Polytechnic Institute. His medical degree was received from the University of Pennsylvania Medical School in 1953. Currently, he is interning at The Pennsylvania Hospital, Philadelphia.

Eugene M. Gillum, M.D., Indianapolis, wrote on "A Study of the Effect of Smoking on Diabetic Blood Sugars." Doctor Gillum received his Bachelor of Arts degree from Earlham College in 1948 and was graduated in medicine from Indiana University this year. At present, he is an intern at General Hospital, Indianapolis. He spent two summers at the Roscoe B. Jackson Memorial Laboratory, Bar Harbor, Maine, studying animal behavior.

Samuel S. Koide, M.D., Chicago, received his medical degree from Northwestern University Medical School this year. He obtained a Bachelor of Science degree from the University of Hawaii in 1945. Doctor Koide served in the Infantry and Military Intelligence, United States Army, with the rank of first lieutenant. His paper is

entitled "Insulin Requirement in Relation to Mechanism of Hepatic Function in Diabetes." In 1951, he prepared a paper with S. Freeman on the "Effect of Eck Fistula Formation on Alloxan Diabetic Dogs" which was published in the *American Journal of Physiology.*

Walter B. MacGrath, Jr. submitted two papers entitled "The HGF Content of the Pancreas Following Insulin in Normal and Insulin-Resistant Mice" (See "The Effect of Insulin on the Glucagon Content of the Pancreas," page 453.) and "Histochemical Identification of the Cells of the Islets of Langerhans." Mr. MacGrath, a student at Jefferson Medical College in Philadelphia, received a Bachelor of Arts degree from Cornell University in 1949 and a Master of Science degree in 1951 from the University of Massachusetts, where he majored in physiology. In 1950-51 he attended New York Medical College. He also has served as Graduate Teaching Fellow and Teaching Assistant at the University of Massachusetts and Amherst College respectively. Mr. MacGrath received honorable mention in 1951 in the Schering Award Competition. He is an Associate Member of the American Diabetes Association.

Roger M. Morrell, a senior at George Washington University School of Medicine, entitled his paper "Some Relationships of the Pituitary-Adrenal System to Diabetes Mellitus." Mr. Morrell received a Bachelor of Science degree from Haverford College in 1950. He won Second Prize in the Schering Award Competition in 1951 and honorable mention, National League Against Epilepsy in 1953. Co-editor of the Yearbook, "The Speculum," Mr. Morrell likewise was President of Beta Upsilon Chapter of Nu Sigma Nu. He plans to enter the field of neurosurgery.

The Editor and the Editorial Board, on behalf of the Association, offer their congratulations to Mr. Feld and those who received honorable mention.

Members of the American Diabetes Association and subscribers of DIABETES are reminded that there is another contest closing April 1, 1954, open to medical students and physicians within two years after graduation from medical school. They are asked to urge their students and interns to submit papers by that date. Candidates may choose any subject relating to diabetes. The length of the paper may be from six to eighteen pages, typewritten and double-spaced. Manuscripts should be sent to the Editorial Office of DIABETES, 11 West 42nd Street, New York 36, N. Y. The papers will be reviewed by the Editorial Board which, in selecting the best paper, will take into consideration the value of the material and the method of presentation. The prize of $250 is made possible again through the kindness of the St. Louis Diabetes Association.

The Fourteenth Annual Meeting

The next Annual Meeting of the American Diabetes Association will be held in San Francisco on June 19 and 20. Our organization, as in the past, will hold its meeting immediately preceding the Annual Session, June 21-25, of the American Medical Association.

The Fairmont Hotel will serve as headquarters for our Association. Unfortunately, because of restrictions imposed by other organizations, it has been impossible to secure a block of rooms at that hotel for our members. Reservations should be made through the Housing Bureau of the American Medical Association. This information undoubtedly will be printed in the near future in *The Journal of the American Medical Association.*

As announced in the last issue of DIABETES, physicians and other scientists are invited by Henry T. Ricketts, M.D., Chairman of the Association's Committee on Scientific Programs, to submit abstracts of papers which they would like to present at the Scientific Sessions. Persons interested are requested to present seven copies of the abstract to facilitate review by the Committee.

Research Fellowships of the American Diabetes Association

The need for a research program of the American Diabetes Association has been recognized for many years. Although the Association's resources are limited at present, the Council appropriated $5,000 to the Committee on Research for such a program.

Two fellowships of approximately $2,500 each are

therefore available this academic year for adequately trained investigators who will give their full time to a problem in the general field of diabetes in the laboratory or clinic of a recognized authority on this subject. Applications should be sent to the Executive Director, the American Diabetes Association, 11 West 42nd Street, New York 36, N. Y.

New Members

The following Active Members were elected as of November 1 and December 1, 1953:

California

Karstens, Hans Carsten	San Diego
Kent, James E.	Corona
Ross, Ralph D.	Corona
Woodbridge, John H.	San Luis Obispo

District of Columbia

Thompson, Jr., J. Lawn	

Illinois

Sluzynski, Leonard S.	Chicago

Indiana

Osterman, Louis H.	Seymour

Maryland

Gibbs, Gordon E.	Baltimore

Massachusetts

Barclay, Jr., Paul L.	Brookline
Lavelle, Gertrude H.	Natick
Pirone, Francis A.	Lynn

Michigan

Stewart, Lewis L.	Jackson

Minnesota

Johnson, Herbert W.	St. Paul

New Jersey

Crandall, John K.	Fort Lee
Dresel, Irmgard	Far Hills
Rainey, Willard G.	Princeton

New York

Brandt, J. Leonard	Brooklyn
Helman, Charles H.	Bronx
Hershkowitz, Melvin	New York
Kohn, Anthony	Islip Terrace
Lewenter, Isaac	New York
Peltz, Charles	Brooklyn
Sarno, Avery H.	Johnstown
Schutzer, Seymour	New York

Ohio

Cohen, Jack R.	Steubenville
Cook, James R.	Cleveland
Deerhake, Homer G.	Lima
Sido, Gregor	Toledo

Pennsylvania

Benz, George H.	Pittsburgh
Beyer, Samuel M.	Punxsutawney
Bloom, Julius	Altoona
Boucek, John J.	Pittsburgh
Cosgrove, Edgar F.	Pittsburgh
Gregg, Frank J.	Pittsburgh
Novak, Joseph F.	Pittsburgh
O'Neill, Francis H.	Pittsburgh
Rhodes, George J.	Pittsburgh
Rowland, Harold A.	Norristown
Skromak, Stanley J.	Philadelphia
Strickland, Wilbur H.	Philadelphia
Wilkins, Daniel M.	Pittsburgh

Texas

Shytles, Jr., Harry M.	Sherman

Wisconsin

Mayer, Hanno H.	Milwaukee
Tufts, Millard	Milwaukee

OTHER COUNTRIES

Canada

Isobelle, Gaston J.	Hull, Que.
Plewes, David F.	Brantford, Ont.

Denmark

Jersild, Mogens	Klampenborg

Venezuela

Roche, Marcel	Caracas

The following Associate Member was elected as of December 1, 1953:

Canada

Sister Miriam Claire	Victoria, B.C.

News of Affiliate Associations

The LOS ANGELES DIABETES ASSOCIATION held its fall Meeting and Symposium on Monday evening, November 30, in the Auditorium of the Los Angeles County Medical Association. The Symposium, moderated by Samuel Soskin, M.D., was on the subject of the "problem" diabetic. Among the participants were Helen Martin,

M.D., and William H. Grishaw, M.D., who discussed aspects relating to internal medicine and pediatrics respectively.

The NEW ENGLAND DIABETES ASSOCIATION held its fall clinical meeting on Monday, November 2. The scientific program was devoted to a review of the problem of surgical lesions of the feet in diabetic patients, based on a study sponsored by the Diabetes Committee of the Massachusetts Medical Society, with the cooperation of a number of Boston hospitals. The medical aspects were presented by Samuel B. Beaser, M.D., and David Hurwitz, M.D. The surgical aspects were presented by Theodore C. Pratt, M.D. Plans for the Diabetes Fair, held in Boston November 16 and 17, were presented by Harry Blotner, M.D.

The NEW JERSEY DIABETES ASSOCIATION, in cooperation with The Medical Society of New Jersey and the New Jersey State Department of Health, presented a Symposium on Diabetes Mellitus, in Newark on October 21. The meeting was opened by Henry B. Decker, M.D., President of The Medical Society of New Jersey, and Doctors Otto Brandman and Everett Bauman served as Chairmen. The speakers and topics were as follows: "Diabetes, A Public Health Problem," Daniel Bergsma, M.D., New Jersey State Commissioner of Health; "Recent Advances in Experimental Diabetes," Francis D. W. Lukens, M.D., of Philadelphia; "Current Treatment of Diabetes Mellitus," Garfield G. Duncan, M.D., of Philadelphia; "Electrolyte Imbalance in Diabetic Acidosis," Thomas Hodge McGavack, M.D., of New York City; "Management of Diabetic Acidosis," Herbert Pollack, M.D., of New York City. A panel discussion was moderated by Elmer L. Sevringhaus, M.D., of New York City, in which the aforementioned speakers participated.

News Notes

Organization of an Endocrine Society in Cuba

La Sociedad Cubana de Endocrinologia was organized in Havana in June, 1953, in order to bring together Cuban physicians interested in this branch of medicine. The directors include Dr. M. D. Cardenas Pupo, President, Dr. Manuel M. Villaverde, Secretary-Treasurer, and Drs. Julio F. Schutte, M. Fuentes Aguilera and Rafael Plasencia.

Personal

At the Seventh Annual Fall Postgraduate Clinic of the Wayne County and Michigan Academies of General Practice in East Lansing, Mich., in November, Julius Pomeranze, M.D., New York City, and Jerome W. Conn., M.D., Ann Arbor, presented papers. Doctor Pomeranze discussed "Newer Therapy in Diabetes Mellitus" and Doctor Conn spoke on the "Physiology of the Adrenal Gland."

George E. Anderson, M.D., Brooklyn, N.Y., spoke to the Easton Lay Group of the Lehigh Valley Diabetes Association on Thursday, November 19, in Easton, Pa., on the subject "Doctor-Patient Relationship in Diabetes".

Herbert Pollack, M.D., New York City, participated in a Symposium on protein metabolism at the University of Toronto on October 30. He discussed amino acids and proteins in therapy.

Obituary

WALTER FERRIER ROGERS, JR., M.D., a member of the American Diabetes Association since 1948, died while at work on September 18 of an acute coronary thrombosis at the age of thirty-five. Only a few of his associates knew that he had been a diabetic since 1934.

After graduating from Hamilton College in 1940 he attended the Syracuse University School of Medicine, becoming a member of Nu Sigma Nu and Alpha Omega Alpha Fraternities. Completing Medical School in 1943, he interned at Rhode Island Hospital, Providence. Successively he became an instructor in the Department of Pathology, Syracuse University; Assistant in Medicine, Boston City Hospital, and Research Fellow in Medicine, Harvard Medical School and of the Thorndike Memorial Laboratory, for two and a half years; and, at the time of his death, was Assistant Professor of Medicine at the State University of New York, Upstate Medical Center, Syracuse, conducting investigation in endocrine and metabolic diseases.

One of his last formal teaching exercises was the presentation of a clinic to first year medical students on the subject of "Diabetes Mellitus, Its Physiology and Complications."

Likewise, he was associate attending physician at Syracuse University Hospital and assistant attending physician, Syracuse Memorial Hospital. He was a member of The Endocrine Society and the American Federation of Clinical Research.

SUBJECT INDEX

This index covers all reading matter in DIABETES. Most entries refer to material in the ABSTRACTS; entries marked with an asterisk (*) indicate articles which appeared in full in DIABETES during 1953. The author index appears on Page 530.

A

ABDOMEN, acute, hyperglycemia with glycosuria and, [Khedroo & DiGilio] 59
simulation in diabetic with membraneous dysmenorrhea, [Treiber & Norton] 314
ACCIDENTS, automobile, hypoglycemia and, [Lawrence] 60
ACETATE, metabolism, in mice, hereditary obesity-diabetes syndrome and, [Guggenheim & Mayer] 398
ACETOACETATE, activity, in rabbit bone marrow, [Evans] 305
ACETOACETIC ACID, determination, [Thin & Robertson] 314
ACETONE, in plasma, simple qualitative test, [Duncan & Gill] *353
in serum, determination, diabetes and, [Page] 227
BODIES: See Ketone bodies
ACIDOSIS: See also Diabetes, acidosis
diabetic, clinical value of a qualitative test for plasma acetone, [Duncan & Gill] *353
diabetic coma and, studies in: interrelationships of urinary potassium, sodium and chloride, [Danowski] 474
diabetic, some medical complications of, [Luikart] 484
effect on glucose uptake, [Mackler & others] 62
effects, on the metabolism of fructose, [Mackler & Guest] 485
effects on utilization of glucose in erythrocytes and leucocytes [Graubarth & others] 479
metabolic, ether anesthesia and, [Brewster & others] 216
potassium in coma, [Crampton & others] *1
ACROMEGALY, diabetes and, [Bach & others] 302
ACTH, action on adrenal slices, [Haynes & others] 222
arthritic lesions and, in vitamin C deficient guinea pigs, [Hughes & others] 58
capillary lesions and, [Friedenwald] 221
changes in eosinophils in juvenile diabetes in response to, [Grinspoon] 479
cortisone with, dwarfism associated with hypoglycemia and convulsions and, [Steiner] 413
development of diabetes during treatment with, [Bookman & others] *100
diabetogenic effects of, acromegaly and, [Bach & others] 302
effects on blood glycolysis, [Vaccari & Rossanda] 68
effects on carbohydrate tolerance and blood glutathione levels, [Joiner] 59
effects on carbohydrate metabolism and serum amylase activity in rheumatoid arthritis, [Tribby] 232
effects on carbohydrate metabolism in hypophysectomized dogs, [de Bodo & others] 147, 394
effects on glyconeogenesis, in diabetics, [Kinsell & others] 402
effects on growth hormone activity, [Reid] 410
effects on insulin sensitivity in hypophysectomized dog, [de Bodo & others] 147
effects on plasma sulfhydryl and protein levels, [Shacter & Entenman] 158
inhibition by potassium chloride enriched diet, [Glafkides & others] 56
pancreatic insular adenoma and, [Osnes & Thorsen] 407
release, desoxycorticosterone acetate and, [Zimmerman & others] 234
sprue and, [Colcher & others] 393
thyroid with, dwarfism associated with hypoglycemia and convulsions and, [Steiner] 413
ADA DIETS, [Behrman] *272
ADA DIETS, [Caso] *275
ADENOSINE-5-MONOPHOSPHATE, effects on serum and aortal lipids, [Milch & others] 153
ARENOSINETRIPHOSPHATE in liver, alloxan diabetes and, [Sacks] 411
spectrophotometric determination, [Slater] 230
ARENOSINETRIPHOSPHATE in liver, alloxan diabetes and, [Sacks] 411
spectrophotometric determination, [Slater] 230
ADP: See Adenosinediphosphate
ADRENAL CORTEX, activity, insulin dosage variation and, [McArthur & others] 62
does glucose stimulate adrenocortical activity? [Schneeberg] *372
effect of adrenal hormones on metabolism of isolated tissue, [Krahl] *26
influence of ascorbic acid on, metabolic action of cortical hormones [Bacchus & Heiffer] 470
function test, [Dury] 395
physiology, carbohydrate metabolism during illness and, [Engel & Burns] 396
physiology, in scurvy, [Stewart & others] 231
pantothenic acid deficiency and, [Hurley & Morgan] 151
studies of the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man, [Burns & others] 472
tumors, Cushing's syndrome and, [Secco] 67
vitamin C and, [Hughes & others] 58
ADRENAL EXTRACTS, effects on growth hormone produced retention of potassium, sodium, chloride, and nitrogen in adrenalectomized rats, [Stein & others] 231
ADRENAL GLAND, ascorbic acid in, in alloxan-injected rats, [Dury] 395
cholesterol, effects of glucose and cold exposure on, [Sterling & Longwell] 413
relationship to the diabetogenic effect of ethylenediamine in the partially depancreatized rat, [Ingle & others] 482
resection, glucose tolerance and, [Sprague & others] 313
secretion, alterations in, as a psychosomatic disorder, [Smolen] 230
slices, action of ACTH on, [Haynes & others] 222
weight, in alloxan-injected rats, [Dury] 395
ADRENALECTOMY, carbohydrate utilization and, effects of diet on, in rats, [Cohn & Kolinsky] 304
effects on fatty acid oxidation, in normal and cortisone-treated animals, [Lipsett & Moore] 405
effects on plasma sulfhydryl and protein levels, [Shacter & Entenman] 158
insulin sensitivity and, [de Bodo & others] 146
ADRENALINE: See Epinephrine
ADRENOCORTICAL STEROIDS: See Steroids, adrenocortical
AGE, coronary heart disease and, [Russell] 411
diabetes and, choline excretion in, [Dowd] 53
diabetes and, therapy, [Dowd] 53
relation to insulin, in a diabetes clinic, [Oppenheimer] 487
serum proteins and, electrophoretic study of, [Rafsky & others] 228
ALBUMIN, synthesis, protein metabolism disturbances in diabetes and, [Schreier & Szybko] 412
ALBUMINURIA, diabetes and, [Lueck] 61

ALCOHOL, effects on blood sugar concentration in alloxan diabetes, [Stirland & Crossen] 232
metabolism, [Newman & others] 64
ALKALI, diabetic coma and, [Duncan] 219
ALLERGIC DISEASES: See Diseases, allergic
ALLERGY, bacterial, carbohydrate metabolism and, [Cornforth & Long] 217
insulin hypoglycemia in, [Weitzner] 70
insulin, [Queries and Minor Notes—Dolger] 489
ALLOXAN, blood pressure and, [MacQueen] 226
desensitizing mechanism, [Cornforth & Long] 217
diabetes, effects of alcohol on blood sugar concentration in, [Stirland & Crossen] 232
diabetes, effects on regeneration of liver phosphatase after lobectomy, [Norberg] 154
diabetes, etiology, [Arteta] 50, [Wachstein] 68
diabetes, in rhesus monkeys, [Ramfjord] 228
diabetes, 17-ketosteroid excretion in, [Koref & Errazuriz] 308
diabetes, liver-phosphate turnover in, [Sacks] 411
diabetes, nephrectomy and, [De Oya & others] 304
diabetes, ocular complications in, [Jane & others] 151
diabetes, ocular damage from microwave irradiation and, [Richardson & others] 66
diabetes, polyuria and sugar excretion in, [Cohen] 52
diabetes, pregnancy of rats with, [Bartelheimer] 471
excretion, in rats and rabbits, [Lee & DeWitt] 404
islands of Langerhans adenoma and, [Bottger & others] 216
metabolism, in rats and rabbits, [Lee & DeWitt] 404
toxic effects, in rhesus monkeys, [Ramfjord] 228
AMINO ACIDS, in plasma, effects of glucose on, in hepatectomized and nephrectomized dogs, [Flock & others] 397
in urine, chromatography of in galactosemia, [Bickel & Hickmans] 144
incorporation into peptides in diabetic tissue, [Krahl] 224
metabolism, in diabetes, [Schreier & Szybko] 411
AMINOACIDURIA in childhood: cystinuria and cystinosis, [Eberlein] 476
AMITHIOZONE, carbohydrate metabolism disturbance and, [Escovitz] 148
AMPHETAMINE, blood sugar and, [Queries and Minor Notes—Milton] 489
AMYLASE, alkaline, in plasma, after hepatectomy, [Flock & others] 148
constancy of ratio of, to protein nitrogen concentration, [Guth & others] 480
in blood, acute pancreatitis and, [Foreign Letters] 306
in serum, acute pancreatitis and, [Foreign Letters] 306
in serum, effects of ACTH on, [Tribby] 232
in serum, pancreatectomy and, [Nardi] 64
pancreatic, phototurbidimetric determination of, [Guth & others] 480
serum, physiologic significance after pancreatectomy in man, [Honjo & Araki] 481
AMYLOIDOSIS, primary, diabetes and gastro-intestinal hemorrhage and, [Pocock & Dickens] 310
AMYLOPECTINS, structure, determination, [Illingworth & Cori] 400; [Illingworth & others] 400; [Larner & others] 403
ANALGESIA, caudal, in various conditions, [Galley] 397
ANASTOMOSIS, splenorenal, in hemochromatosis associated with portal hypertension, [Dunlap & others] 54
ANDROGENS, diabetic severity and, [Lopis & others] 61
ANESTHESIA, liver physiology and, [Child & Payne] 145
metabolic effects, [Brewster & others] 216
ANEURYSMS, retinal, diabetes and, [Friedenwald] 221; [Hartford] 399
ANGINA PECTORIS, heparin in, [Engelberg] 148
ANNUAL MEETING, 1953, program *247
report *335
1954, announcement of, 509
ANTIBODIES, allergic, in serum proteins, [Loveless & Cann] 225
ANTICONVULSANTS, labile diabetes and, [Fabrykant] 397
ANTIHISTAMINICS, nocturnal cramps with diabetes and, [Shuman] 229
ARTERIES: See Blood vessels
ARTERIOSCLEROSIS, cerebral vascular accidents and diabetic acidosis, [Luikart] 484
coronary, diabetes and, [Root & West] 157
coronary, diet in, [Morrison] 227
coronary, heparin in, [Engelberg] 148
coronary, pathogenesis of, [Lober] 484
diabetes and, [Lueck] 61
diabetes and, [Warren] *260
diabetes and, lipids in, [Dewind & others] 395; [Hirsch & others] 307
diet in, reduction of lipoprotein levels and, [Gofman] 56
etiology, essential hyperlipemia and, [Joyner] 400
incidence of peripheral vascular changes in diabetes (Brandman & Redisch] *194
lipids in, [Gofman] 56
pathogenesis, [Hatch] 150
peripheral, heparin in, [Engelberg & Masselli] 221
peripheral, lumbar sympathetic block and lumbar sympathectomy in, [Azar] 470
renal, diabetes and, [Loomis] 405
renal vascular disease in diabetes [Bell] *376
serum lipoprotein and, [Lewis & others] 309
therapy, [Gofman] 56
ARTERIOSCLEROSIS OBLITERANS, therapy, [Texter & others] 232
ARTERIOVENOUS GLUCOSE DIFFERENCES, metabolic hypoglycemia and food intake, [Van Italie & others] 490
ARTERITIS, diabetes and, sodium citrate in, [Foreign Letters] 55
ARTHRITIS, effects of vitamin C on development of, [Hughes & others] 58
rheumatoid, ACTH in, [Tribby] 232
rheumatoid, insulin hypoglycemia in, [Weitzner] 69; [Weitzner & Snowden] 69
rheumatoid, of menopausal women, insulin hypoglycemia in, [Godlowski & Paterson] 56
ARTICHOKES, carbohydrates of tuber, seasonal changes in, [Bacon & Loxley] 303
ASCORBIC ACID, adrenal, in alloxan-injected rats, [Dury] 395
influence on the metabolic actions of cortical hormones, [Bacchus & Heifer] 470
deficiency, effects of insulin on glucose metabolism in, [Stewart & others] 231
ASPIRIN, effects on glycosuria and hyperglycemia, in partially depancreatectomized rats, [Ingle & Meeks] 307
ASTHMA, bronchial, diabetes and, [Gutmann] 398
ATHEROSCLEROSIS: See Arteriosclerosis
diabetes and, [Hamilton] *181
experimental, mast cells and susceptibility to, [Constantinides] 473
relation to serum lipids, [editorial, Ricketts] *316
serum lipids in, [editorial, Ricketts] *316
ATP: See Adenosinetriphosphate
ATROPINE, effect on the electroencephalogram during induced hypoglycemia, [Evarts & others] 477
neurogenic hypoglycemia and, [Queries and Minor Notes] 409
ATROPHY, insulin administration and, [Queries and Minor Notes] 310

B

BAL, diabetic neuritis and, [Sparks] 230
diabetic polyneuritis and, [Guthrie] 150
BALLISTOCARDIOGRAM, effects of heparin on, [Engelberg] 148
BANTING MEMORIAL LECTURE, 1953, pathology of diabetes, [Warren] *257
BAYER, 205, effects on regeneration of liver phosphatase after lobectomy, [Norberg] 154
BELLADONNA, neurogenic hypoglycemia and, [Queries and Minor Notes] 409
BENEDICT, STANLEY ROSSITER, biographical note, [Pollack] *420
BERNARD, CLAUDE, biographical note, [Olmsted] *162
BEST INSTITUTE, formal opening of, *431
BILIARY TRACT, diseases, acute pancreatitis and, [Bockus & others] 392
diseases, diabetes and, [Twiss & Carter] 233

BIOGRAPHICAL NOTES
Willis, Thomas, [Allan] *74
Bernard, Claude, [Olmsted] *162
Lusk, Graham, [Striker] *242
Laguesse, Gustave Edouard, [Hoet] *322
Benedict, Stanley Rossiter, [Pollack] *420
Folin, Otto, [Marble] 503
BIOXILASE: See Cocarboxylase
BLADDER DYSFUNCTION in diabetes, [Spring & Hymes] *199
BLINDNESS, diabetes and, [Minton] 63
BLOOD, determinations as laboratory aids to diagnosis, [Koch] 59
glycolysis, alarm reaction and, [Vaccari & Rossanda] 68
glycolysis, effects of diabetic acidosis on, [Kydd & others] 403
insulin content in diabetes [Boernstein] 472
nonfixation of carbondioxide into organic acids in, [Williams & others] 490
glycolysis, effects of drugs on, [Vaccari & Rossanda] 68
oxygen tension of, effects on normal and diseased retinal vessels, [Sicker & Hickam] 412
volume, polycythemia in retinal venous thrombosis and, [Birge] 144
BLOOD PRESSURE, alloxan and, [MacQueen] 226
high, diabetes and, sodium citrate in, [Foreign Letters] 55
high, hemochromatosis and, [Dunlap & others] 54
high, retinal blood vessel responses to blood oxygen tension changes in, [Sicker & Hickman] 412
low, diabetes and, [Berner] 216
BLOOD SUGAR: See also Hyperglycemia; Hypoglycemia
cataract development in diabetic rats and, [Patterson] 408
clinical usefulness of the Wilkerson-Heftmann test, [Margolin & Gentry] *285
concentrations, regulation of HGF seccretion and, [Foa & others] 221
determination, methods, [Correspondence] 394; [Salo] 229; [Tonks] 232; [Vere] 314
dextroamphetamine and, [Queries and Minor Notes—Milton] 489
diabetes and, [Allen] 215
duodenal ulcer and, [Queries and Minor Notes] 228
effects of alcohol on, [Stirland & Crossen] 232
effect of amount and type of protein in breakfasts on, [Addison & others] 469
effect of amphetamine, [Queries and Minor Notes—Milton] 489
effects of breakfast protein source on, [Coleman & others] 393
effects of growth hormone on, in hypophysectomized rats, [Park & others] 407
effects of HGF on, [Kibler & others] 401
effects of insulin on, in adrenalectomized dogs pretreated with pituitary growth hormones, [Lazarus & Volk] 225
epinephrine and, in sheep, [Zarrow & others] 234
fetal, regulation, [Villee] 315
hypoglycemic manifestations and relation to blood sugar levels [Revitch] 489
hypothalamic lesions and, [Beattie & Chambers] 390; [Mayer & others] 226
BLOOD SUGAR, in the hamster during arousal from hibernation, [Lyman & Leduc] 484
insulin and, in sheep, [Zarrow & others] 234
insulin-glucose tolerance test and effect of insulin dose on decline rate, [Volk & Lazarus] 414
insulin-glucose tolerance test and, in patients with pituitary gland disease, [Soffer] 313
newborn infants and, [Book Review] 145; [Creery & Parkinson] 394
pituitary dwarfism in mice and, effects of fasting on, [Mirand & Osborn] 406
plasmodium berghei infections in rats and, [Mercado] 406
postprandial, diabetes therapy and, [Bohan & others] 392
rapid estimation with Galatest reagent, [Guest & Lestradet] *350
scurvy and, effects of insulin on, [Stewart & others] 231
stress and, [Hinkle & Wolf] 307
test, renal threshold and, [Robinson & Baker-Bates] 156
BLOOD VESSELS, cerebral, sugar concentration of, desoxycorticosterone glucoside and, [Schieve & Wilson] 157
coronary, lipid composition of normal and diabetic, [Lundbaek & Petersen] 309
diseases, diabetes and, [Keiding & others] 152; [Ricketts] 156
diseases, diabetes and, serum polysaccharides in, [Berkman & others] 391
diseases, sodium citrate in, [Foreign Letters] 55
diseases, vasodilator effects of procaine in, [Jessar & others] 223
filtration properties after excision, [Wilens & McCluskey] 233
insufficiency, hydergine in, [Roberts & others] 228
peripheral, diseases, hydergine in, [Roberts & others] 228
BODY, composition, changes during disease, [Moore & others] 63
BONE MARROW, acetoacetate and esterase activity in, [Evans] 305
effect of insulin hypoglycemia on activity of, [Mackenzie Shattock & Micklem] 62
BOOK REVIEWS, A Textbook of Pathology, E. T. Bell *419
Cardiovascular-Renal Disease in Diabetes Mellitus, Sverre Aarseth, *501
Claude Bernard and the Experimental Method in Medicine, J. M. D. Olmsted & E. Harris Olmsted *164
Connective Tissue: Transactions of the Third Conference, Edited by Charles Ragan *329
Diabetic Glomerulosclerosis, Harold Rifkin, Louis Leiter & James Berkman *79
Diseases of the Endocrine Glands, Louis J. Soffer, J. Lester Gabrilove, Henry Dolger & Arthur R. Sohvil *419
Diseases of Metabolism, edited by Garfield G. Duncan *245
Endocrine Treatment in General Practice, edited by Max R. Goldzieher & Joseph W. Goldzieher *244
Experimental Atherosclerosis, Louis N. Katz & Jeremiah Stamler *329
Hormonal Factors in Carbohydrate Metabolism, Volume VI, edited by G. E. W. Wolstenholme, Jesse S. Freeman *329
Liver Injury: Transactions of the Tenth Conference, May 21-22, 1951. F. W. Hoffbauer, Editor *80
Long-Term Diabetes, Knud Lundbaek & Viggo A. Jensen *500
Memento du Diabetique, French Association of Diabetics *246
Nutrition and Diet in Health and Diseases, James S. McLester & William J. Darby *244
Proximate Composition of American Food Materials, U.S. Government Printing Office *245
The Action of Insulin, Niels Haugaard & Julian B. Marsh *502
The Diabetic Neuropathies, Joseph I. Goodman, Siegfried Baumoel, Leonard Frankel, Louis J. Marcus & Sigmund Wasserman *418
Treatment of Diabetes Mellitus, Elliott P. Joslin, Howard F. Root, Priscilla White, & Alexander Marble *78
BRAIN, hypothalamus, congenital defect causing dwarfism, [Steiner] 413
hypothalamus, lesions, blood sugar and food intake in, [Mayer & others] 226
hyopthalamus, lesions, blood sugar in, [Beattie & Chambers] 390
BRAIN DAMAGE, as possible cause of diabetes, [Aarseth] 302
BREAKFASTS, proteins in, effects on blood sugar level, [Coleman & others] 393
BREAST, cancer, relation to diabetes and thyroid disease, [Report] 311
BRITTLE DIABETES, development following pancreatectomy for retroperitoneal leiomycosarcoma, [Nardi] 64
globin zinc insulin in, [Revell] 155
BRUCELLOSIS, complications, [Leon & Aguirre] 404
diabetes and liver deficiency with, [Leon & Aguirre] 404
BUERGER'S DISEASE, hydergine in, [Roberts & others] 228
BURNS, therapy, lactosuria and, [Baar & Bull] 302

C

CALCIUM N-CYCLOHEXYLSULFAMATE: See Sucaryl
CALORIES, intake in obese women, [Beaudoin & Mayer] 216
CAMPS, for diabetic children, [Henson & Heffner] 399; [Lawrence] 403; [Sweeney] 68

CANCER: See also under organ or region affected
diabetes and, mortality, [Foreign Letters] 149
CANINE DIABETES, spontaneous, [Ricketts & others] *288
CANNED FRUITS, noncaloric sweeteners in, [Anderson & others] 469
CAPILLARIES, fragility, diabetic retinopathy and, [Friedenwald] 221
lesions in diabetes, adrenal cortical function and, [Friedenwald] 221
CARBOHYDRATES, cataracts caused by, [Patterson] 488
deficiency, effects on fatty acid formation from acetate carbon, [Lyon & others] 153
in Jerusalem artichoke tubers, seasonal changes in, [Bacon & Loxley] 303
influence of ascorbic acid on metabolic action of cortical hormones, [Bacchus & Heiffer] 470
lens metabolism and, [Nordman & Mandell] 407
metabolism, adrenal cortex and, during illness, [Engel & Burns] 396
metabolism, adrenalectomy and, (Cohn & others] 53
metabolism, bacterial allergy and, [Cornforth & Long] 217
metabolism, diet and, in adrenalectomized rats, [Cohn & Kolinsky] 304
metabolism, disturbances, [Najjar] 227
metabolism, disturbances, amithiozone therapy in pulmonary tuberculosis and, [Escovitz] 148
metabolism, disturbances, isoniazid therapy in pulmonary tuberculosis and, [Evans & Stradling] 396
metabolism, disturbances, liver diseases and, [Leevy & others] 225
metabolism, disturbances, liver phosphate turnover and, [Sacks] 411
metabolism, disturbances, pancreatic disease diagnosis and, [Machella] 405
metabolism, effects of ACTH and cortisone on, in hypophysectomized dogs, [de Bodo & others] 147, 394
metabolism, effects of ACTH on, [Tribby] 232
metabolism, effects of adrenal cortical extract on, in hypophysectomized dogs, [de Bodo & others] 147, 394
metabolism, effects of adrenaline and noradrenaline on, [Walaas & Walaas] 414
metabolism, effects of adrenocortical steroids on, in hypophysectomized dogs, [de Bodo & others] 147, 394
metabolism, effects of Raben-Westermeyer growth hormone on, [Conn & others] 217
metabolism, fat synthesis and, thiamine deficiency and, [Gruber] 57
metabolism, growth hormone and, [Editorial] 219
metabolism, in kidneys, [Dratz & Handler] 395
metabolism in man, studies of the interdependent effects of stress and the adrenal cortex on, [Burns & others] 472
metabolism, insulin and, [Bruch] 217
metabolism, pantothenic acid deficiency and, [Hurley & Morgan] 151
metabolism, physiology, [Najjar] 227
metabolism, prediabetic mother and, [Futcher & Long] 222
metabolism, surgical convalescence and, [Hayes & Brandt] 150
tolerance, blood glutathione levels and effects of ACTH on, [Joiner] 59
tolerance, hyperglycemia in diabetic and, [John] 59
CARBON DIOXIDE, in plasma, determination, diabetes and, [Page] 227
CARDIOVASCULAR DISEASE: See Heart
CASTRATION, diabetes and, in partially pancreatectomized rats, [Rodriguez] 311
CATARACTS, diabetes and, [Givner]
CATARACTS, caused by carbohydrates, [Patterson] 488
diabetes and, [Givner] 222; [Marr] 62; [Minton] 63
diabetes and, extraction, [de Ocampo] 227
diabetes and, prognosis, [Cordes] 217
experimental, blood sugar and, in diabetic rats, [Patterson] 408
fishlens protein extracts in, [Shropshire & others] 67
formation, nicotinic acid and, [Janes & others] 151
galactose and, [Patterson] 488
galactosemia and, [Patz] 408
glucose and, [Patterson] 488
CEREBRAL dysrhythmia, pseudohypoglycemic reactions and, in diabetes mellitus, [Musser & others] 487
CELLS, glucose absorption by, in diabetic and normal subjects, [Lestradet] 404
CEREBROSPINAL FLUID, glucose in, determination, [Webb & Isaac] 414
glucose in, determination, diagnostic value of, [Webb & Isaac] 414
protein content in diabetes and, [Madonick & Magolis] 226
CERULOPLASMIN, in serum, in Wilson's disease, [Scheinberg & Gitlin] 67
CESARIAN SECTION, diabetic pregnancy and, [Pedowitz & Shlevin] 155
CHARCOT'S JOINT, diabetes and, [Martin] 153; [Paul] 227
CHLORIDE, retention, growth hormone and, in adrenalectomized rats, [Stein & others] 231
CHOLESTEROL, absorption, factors influencing, [Kim & Ivy] 224
arteriosclerosis and, [Morrison] 227
consumption, cardiovascular disease mortality and, [Pihl] 64
effect on lipoprotein concentration, in hypothyroid dogs, [Lewis & others] 309
formation from C14 acetate in fasting rat, [Van Bruggen & others] 314
relation of hypercholesterolemia to atherosclerosis, [Hamilton] *181
in blood effect of insulin coma therapy in schizophrenic patients on, [Goodman & Kanter] 56
in blood, thrombosis of central retinal vein and, [Cascio] 217
in food, [Pihl] 65
in serum, absorption by montmorillonite, [Nikkilä & Oker-Blom] 227
in serum, cholic acid and, [Kim & Ivy] 224
in serum, diabetic children and, [Dine & Jackson] 305
in serum, diabetic glomerulosclerosis and, [Engelberg & others] 220
in serum, effects of hepatectomy on, [Lewis & others] 404
in serum, in juvenile diabetes, [Dine & Jackson] *206
metabolism, effects of *a*-cells of islets of Langerhans on, [Francisco] 56
synthesis, in diabetic liver, effects of insulin on, [Hotta & Chaikoff] 399
synthesis, in liver, [Werthessen & Schwenk] 233
synthesis, in liver, effects of fasting and diet on, [Chaikoff & Tomkins] 145
synthesis, in liver, effects of hypophysectomy on, [Tomkins & others] 414
CHRONIC DISEASE, causes of disability in patients with, [Goodman] 479
CHOLINE, excretion, diabetic classification and, [Dowd] 53
lipotropic action, [Elvehjem] 220
CITRATE, formation, effects of fluoroacetate on, in rat liver and kidney tissue, [Busch & Potter] 145
CITRIC ACID, in serum, effects of insulin on, in schizophrenia, [Gottfried & others] 398
CLAUDICATION, intermittent, in arteriosclerosis obliterans, therapy, [Texter & others] 232
time, in arteriosclerosis obliterans, therapy, [Texter & others] 232
COCARBOXYLASE, diabetic acidosis and, [Klinger & Dalle Coste] 402
diabetic complications and, [Klinger & Dalle Coste] 402
COENZYME A, mechanism of action, [Lipsett & Moore] 404; [Seaman] 312
COLD, exposure, effects on adrenal gland cholestrol after glucose administration, [Sterling & Longwell] 413
COLON, obstruction, pancreatitis and, [Miln & Barclay] 63
COMA: See Diabetes, coma
COMMITTEES OF ADA, 1953-54 *427
COMMITTEE REPORTS, camps, [Marble] *334
detection and education, [Reed] *165, *333, *426
employment, [Beardwood] *333
postgraduate education, [Bortz] *334
COMPLICATIONS, of diabetes, acute, [Colwell] *267
COPPER, metabolism, in Wilson's disease, [Scheinberg & Gitlin] 67
CORD BLADDER, in diabetes, [Spring & Hymes] *199
CORTICOSTEROIDS, output by adrenals, ACTH and, [Haynes and others] 222
CORTICOTROPIN: See ACTH
CORTISONE, ACTH with, dwarfism associated with hypoglycemia and convulsions and, [Steiner] 413
arthritic lesions and, in vitamin C

deficient guinea pigs, [Hughes & others] 58
capillary lesions and, [Friedenwald] 221
desensitization, carbohydrate metabolism in bacterial allergy and, [Cornforth & Long] 217
diethylstilbestrol with, effects on normal force-fed rats, [Ingle] 400
development of diabetes during treatment with, [Bookman & others] *100
effects on blood glycolysis, [Vaccari & Rossanda] 68
effects on carbohydrate metabolism, in hypophysectomized dogs, [de Bodo & others] 147, 394
effects on fatty acid oxidation, in adrenalectomized animals, [Lipsett & Moore] 405
effects on glyconeogenesis, in diabetics, [Kinsell & others] 402
effects on insulin sensitivity in hypophysectomized dog, [de Bodo & others] 147
effects on metabolic response to injury, [Engel & Burns] 396
effects on normal force-fed rats, [Ingle] 400
effects on plasma sulfydryl and protein levels, [Shacter & Entenman] 158
glycogen deposition in different skeletel muscles induced by, [Leonard] 483
glycosuria induced by, effects of salicylate on, [Smith] 230
hyperglycemia induced by, effects of salicylate on, [Smith] 230
insulin antagonism and, [Stetten] 313
pancreatic insular adenoma and, [Osnes & Thorsen] 407
sprue and, [Colcher & others] 393
studies of the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man, [Burns & others] 472
temperature effects on, [Scherr] 229
COUNCIL MEETING, 1953, *251
COXSACKIE VIRUS, damage to pancreas and, [Wachstein] 68
COXSACKIE VIRUS INFECTION, hypoplasia of pancreatic tissue and, [Lumb & Beautyman] 226
CUSHING'S SYNDROME, [Sprague & others] 313
diabetes and, [Secco] 67; [Sprague & others] 313
N-CYCLOHEXYLSULFAMATE, CALCIUM: See Sucaryl
CYSTEINE, diabetic retinitis and, [Niedermeier] 407
hemorrhagic retinitis and, [Niedermeier] 407
CYSTINURIA, and cystinosis, [Eberlein] 476

D

DEATH, causes in diabetes, [Warren] *260
DEATHS, Collins, James R. *432
Grice, Harold I. *432
Hirsh, Joseph Emmett *170
Nadler, Walter H. *170
Paul, John Davis *432
Reiners, Charles Robert *170
Rogers, Jr., Walter Ferrier, 511
DEHYDRATION, diabetic coma and, [Moreau & others] 153; [Stephens & Root] 413
DEHYDROASCORBIC ACID, diabetes production by destruction of β-cells of islands of Langerhans with, [Wachstein] 68
DERMATITIS: See Skin, diseases
DESENSITIZATION, mechanism, carbohydrate metabolism and, [Cornforth & Long] 217
DESOXYCORTICOSTERONE, arthritic lesions and, in Vitamin C deficient guinea pigs, [Hughes & others] 58
DESOXYCORTICOSTERONE ACETATE, effects on eosinophils during insulin shock therapy, [Zimmerman & others] 234
DESOXYCORTICOSTERONE GLUCOSIDE, cerebral venous sugar concentration and, [Schieve & Wilson] 157
effects on renal tubular reabsorption of glucose, [Despopoulos & Kaufman] 53
DEXTROSE, rapid injections of, [Frost & others] 149
tolerance, compared to invert sugar tolerance, [Frost & others] 149
DIABETES, acidosis, blood in, [Kydd & others] 403
acidosis, cocarboxylase in [Klinger & Dalle Coste] 402
acidosis, effects on glycolysis in blood, [Kydd & others] 403
acidosis, electrolytes in, during recovery, [Darrow & Pratt] 218
acidosis, electrolytes in plasma and erythrocytes during, [Nichols & Nichols] 310
acidosis, hyperlipemia and, [Harris & others] 306
acidosis, insulin resistance and, [Robillard] 411
acidosis, physiology, [Carreras] 145
acidosis, pregnancy in: See Pregnancy, diabetes and, acidosis
acidosis, prophylaxis, [Lueth & Freidell] 226
acidosis, serum lipids in, [Harris & others] 306
acidosis, therapy, [Carreras] 145; [Lueth & Freidell] 226; [Nichols & Nichols] 310; [Stephens & Root] 413
acidosis, water in, during recovery, [Darrow & Pratt] 218
acidosis, water in plasma and erythrocytes during, [Nichols & Nichols] 310
acromegaly and, [Bach & others] 302
adjustments of patient to, [Gibson] 222; [Robinson & Walker] 311
albuminuria and: See Albuminuria
alloxan: See Alloxan, diabetes
amino acid metabolism in [Schreier & Szybko] 411
amithiozone in development of [Escovitz] 148
arteriosclerosis and: See Arteriosclerosis
as a psychosomatic disorder, [Smolen] 230
associations: See also Diabetic Association; International Diabetes Federation [Lawrence] 403
biliary tract diseases and, [Twiss & Carter] 233
blood pressure in: See Blood pressure
brain damage as cause of, [Aarseth] 302
breast cancer and, [Repert] 311
brucellosis and: See Brucellosis
camps for children: See Camps
care of infant of diabetic mother, [Queries and Minor Notes—Bolinske] 488
case finding in two Ontario communities, [Kenny & Chute] *187
cataracts in: See Cataracts
cerebrospinal fluid in, protein content of, [Madonick & Magolis] 226
Charcot's joint and: See Charcot's joint
chart, [Robinson & Baker-Bates] 156
coma, [Dejean] 475
coma, and its treatment, [Moreira] 486
coma, clinical features, [McCullagh] *171
coma, clinical value of a qualitative test for plasma acetone [Duncan & Gill] *353
coma, dehydration in, [Moreau & others] 153; [Stephens & Root] 413
coma, extreme insulin resistance in, [Rose, Kaplan & Picard] *462
coma, fatal, insulin-resistant following insulin therapy in rheumatoid arthritis, [Simpson & Trowbridge] 490
coma, fluid and electrolyte balance in, [Mach] 485
coma, following excessive consumption of carbohydrate with recovery from diabetes, [del Greco & Scapellato] *457
coma, in a case of transient diabetes following short-term excessive consumption of carbohydrate [del Greco & Scapellato] *457
coma, in children, mortality, [Foreign Letters] 149
coma, insulin in, [Stephens & Root] 413
coma, insulin resistance in diabetic, [Rose, Kaplin & Picard] *462
coma, mortality, [McCullagh] *172
coma, pathologic physiology and treatment, [Duncan] 475
coma, potassium in, [Fajans] 397
coma, potassium therapy, [Pollack] *179
coma, renal function and, [Bernstein & others] 51
coma, therapy, [Azerad & Alagille] 144; [Duncan] 219; [Fajans] 397; [Moreau & others] 153; [Stephens & Root] 413
coma, treatment, [Crampton & others] *1
coma, treatment, [Moreira) 486
coma, treatment of, [Pollack] *177
complications: See also specific diseases
complications, [Brousseau] 392
complications of, [Editorial] 476
complications, therapy, [Klinger & Dalle Coste] 402; [Sparks] 230
Cushing's syndrome and: See Cushing's syndrome
decreased activity and energy balance in the hereditary obesity-diabetes syndrome of mice, [Mayer] 486
degranulation of the beta cells in the islets of Langerhans in, [Bell] *125

destruction of β-cells of islands of Langerhans in etiology of, [Wachstein] 68
detection of mild diabetes by feeding glucose to induce glycosuria, [Futcher & Sauvé] *31
development during treatment with cortisone and corticotropin, [Bookman & others] *100
diabetic diet exchange lists, [Caso] 472
diabetic screening test, [Futcher & Sauvé] *31
diagnosis, [Allen] 302; [Kodousek & Endrys] 402; [Reed] 311; [Thosteson] 314
diagnosis, differential, [Amatuzio & others] 390; [Queries and Minor Notes] 311
diagnosis of, [Hollis & Hurst] 481
diagnosis, in general practice, [Bicknell] 303
diagnosis, insulin-glucose tolerance test and lymphocyte count and, [Volk & Lazarus] 315
diet: See Diet
Di-Insulin-Novo in, [Kaechele & Petrides] 400
duodenal ulcer and: See Duodenal ulcer
dysmenorrhea and: See Dysmenorrhea
education of the diabetic, [Downie] 54; [Gibson] 222
effects of cold on partially depancreatized rats, [Ingle & others] *122
effects of environment on, [Ingle & others] *122
effects of hormones on development of, [Lopis & others] 61
electroencephalogram of diabetics, [Izzo & others] *93
eosinophils in, [Kjems] 225
etiology, [Aarseth] 302; [Bach & others] 303; [Evans & Stradling] 396; [Leon & Aguirre] 404
experimental: See also Obesity-diabetes syndrome
experimental, action of estrogens in, [Acevado & Migone] 469
experimental, estrogens and, [Rodriguez] 312
experimental, growth hormone and, [Editorial] 220
experimental, mechanism, [Stetten] 313
eyes: See Blindness; Cataracts; Eyes; Glaucoma; Lipemia retinalis; Retina; Retinitis; Retinopathy; Rubeosis iridis
foot lesions, management, [Miller] 63
following total pancreatectmy in man, [Gourevitch] 479
formaldehydogenic steriod excretion in, [Wolfe & Paschkis] 70
from pancreatectomy in man, [Honjo & Araki] 481
fructose and glucose metabolism in, [Smith & others] 312
fructose metabolism by liver in, [Craig & others] 146
gallbladder and: See Gallbladder
gangrene, lumbar sympathetic block and lumbar sympathectomy in, (Azar] 470
group therapy, [Goodman & others] *280
growth and development of children with, [Jackson] *90
growth hormones and, [Mayer & Silides] 309
heart disease and: See Heart, disease
heredity and: See Heredity
history, [Reviews] 66
hospital for diabetics, [Editorial] 305
hyperglycemia and: See Hyperglycemia
impotence in, [Queries and Minor Notes] 155; [Schept] 229
in children, [Chute] *268
in Iceland, [Albertsson] *184
in industry, [Brandaleone & Friedman] *448
in infants, [Farrell & others] *85
in infants and children, blood pyruvic acid in, [Passweg] 64
in infants and children, cataracts in, [Marr] 62
in infants and children, management, [Daeschner] 146; [Jackson] 308
in infants and children, retinopathy in, [Marr] 62; [Siegel] 230
in physicians, [Mirsky & others] 226
incidence: See Diabetes, statistics
infections: See Infections
in the dog, spontaneous, [Ricketts & others] *288
insulin-resistant, associated with hemochromatosis, [Eskind & others] 477
isocaloric diet in management, [Anderson] 470
isoniazid in, [Correspondence] 394
Kaposi's sarcoma and, [Ronchese & Kern] 312
kidneys in: See Kidneys
labile, anticonvulsants in, [Fabrykant] 397
labile, electroencephalography in, (Fabrykant] 397
lipemia retinalis and, [Nadbath & Fauteux] 64
liver diseases and: See Liver diseases
management of, [Dolger] 475
mass screening with St. Louis Dreypak (a device for the collection of dried urine specimens) [Olmsted & others] *37
mechanism, [Lestradet] 404
modern treatment, [Ricketts] 490
mortality: See Diabetes, statistics, mortality
muscular atrophy and, [Hirson] 399
myelopathy, [Garland & Taverner] 478
nephrosis and: See Nephrosis
neurogenic bladder dysfunction in [Spring & Hymes] *199
neurologic complications: See Nervous system; Neuritis; Neuropathy
neuropathy, [Hirson & others] 481
nocturnal cramps in, [Shuman] 229
nutrition in: See Nutrition
obesity and: See Obesity
ocular changes in and their effect on the patient's vision, [Cordes] 473
ophthalmological aspects, [Marks] 485
pancreatic, [Twiss & Carter] 233
panhypopituitarism and, Raben-Westermeyer growth hormone in, [Conn & others] 217
papillary necrosis and: See Necrosis
paramyloidosis and gastrointestinal hemorrhage and, [Pocock & Dickens] 310
pathology of, [Warren] *257
pathogenesis of, [Bartelheimer] 471
peripheral vascular changes in, [Brandman & Redisch] *194
polyarteritis nodosa presenting as, [French] 478
potassium metabolism in, [Aikawa & others] 215
pre-diabetic state in parents of overweight babies [editorial, McCullagh] *160
pregnancy in: See Pregnancy
prognosis, [Rippy] 156
progress, [Lockwood] 309; [Striker] 413
protein metabolism in, [Editorial] 395
public health interest in [Ford] 477
record incidence in Australia, [Foreign Letters] 478
renal vascular disease in, [Bell] *376
results of a screening program, [Harwood] *43
retinopathy, [Murphy] 487
retinal blood vessel responses to blood oxygen tension changes in, [Sieker & Hickam] 142
review, [Annotations] 143; [Beaser] 50; [Striker] 413
serum acetone determination in, [Page] 227
serum cholesterol, in children, [Dine & Jackson] 305
serum cholesterol, in juvenile diabetes [Dine & Jackson] *206
serum polysaccharides in, [Berkman & others] 391
serum protein turnover in, [Forker & Chaikoff] 149
sex and: See Sex
sialolithiasis and, [Bartelheimer] 215
similarity to starvation, [Stetten] 313
skin manifestations in: See Skin
social aspects of, [Grunberg & Blair] *277
spontaneous remission after coma and extreme hyperglycemia, [Cheng & others] 473
statistics, incidence, in families with allergic diseases, [Gutmann] 398
statistics, mortality, causes, [Foreign Letters] 149
statistics, report of Committee on Statistics, [Marks, chairman] *325
"Steroid," relationship of potassium to, [Kinsell] 482
stress and, [Hinkle & Wolf] 307
studies in diabetic coma and acidosis, interrelationships of urinary potassium, sodium and chloride, [Danowski] 474
surgery in, [Azar] 470
symptoms, prodromal, [Allen] 302
therapy, [Beardwood & others] 303; [Bohan & others] 392; [Boldt & Boldt] 392; [Editorials] 54, 396; [Essellier & others] 396; [Greenhouse] 57; [Lawrence & Oakley] 403; [Revell] 155
therapy, in general practice, [Bicknell] 303; [Downie] 53; [Odom] 407; [Robinson & Walker] 311; [Thosteson] 232
therapy, in mental hospitals, [Ross & Gibson] 67
therapy, objectives, [Ricketts] 156, 228
therapy, prophylaxis of vascular complications and, [Keiding & others] 152

therapy, review, [Haunz] 222
300 years ago, [Allan] *74
thrombosis of central retinal vein and, [Cascio] 217
transient, following a short-term excessive consumption of carbohydrate, [del Greco & Scapellato] *457
transitory, etiology, [Barnbrook] 50
treatment of [Colwell] *262
tuberculosis and: See Tuberculosis
types, differentiation, [Queries and Minor Notes] 311
undernutrition treatment, (Queries and Minor Notes—Jones] 489
urinary tract infections and, [Barnard & others] 215
vitamin deficiency in, [Beidleman] 303
with Friedreich's ataxia in sisters, [Ashby & Tweedy] 470
with obesity, [Richardson] *454
DIABETES CONTROL, [editorial, Bortz] *235
DIABETES DETECTION DRIVE, in Connecticut, [Hart] 58
[Margolin] *424
1952, *81
[Reed] *426
induction of hyperglycemia by feeding glucose, [Greene & others] *299
DIABETES FAIR, [Blotner] *47
Diabetes Week, [Editorial] 395; [Reed] 311
DIABETIC acidosis, clinical features, [McCullagh] *171
DIABETIC ASSOCIATION, in England, [Lawrence] 403
DIABETIC NEUROPATHY, diabetic bladder dysfunction, [Spring & Hymes] *199
DIABETIC NOSTRUMS AND QUACKERY, [editorial, Ricketts] *72
DIABETIC RETINOPATHY, [editorial, Friedenwald] *237
RETINOPATHY, [Warren] *260
DIABETICS, employment of [Brandaleone & Friedman] *448
DIABETOGENIC ACTION of different preparations of growth hormone, [Houssay & Rodriguez] 482
DIABETOGENIC EFFECT of ethylenediamine, relationship of the adrenal glands to, in the partially depancreatized rat, [Ingle and others] 482
DIABETOGENIC SUBSTANCES: See also specific substances
hemolyzing action of, [Maske & Wolff] 405
DIAGNOSIS, clinical usefulness of the Wilkerson-Heftmann blood sugar test, [Margolin & Gentry] *285
detection of hidden diabetes by feeding glucose to induce hyperglycemia [Greene & others] *299
DIBENZYLINE, arteriosclerosis obliterans and, [Texter & others] 232
DIET, arteriosclerosis and, [Morrison] 227
daily allowances recommended by Food and Nutrition Board, NRC [Pollack] *497
diabetic, [Boldt & Boldt] 392; [Greenhouse] 57; [Lestradet] 483
effects on cholesterol synthesis by the liver, [Chaikoff & Tomkins] 145
effects on hereditary obesity-diabetes syndrome in mice, [Mayer & others] 406
fat, lipemia retinalis and, [Everett] 221
instructions for the diabetic, [Behrman] *271
isocaloric, in management of diabetes mellitus, [Anderson] 470
neurogenic hypoglycemia and, [Queries and Minor Notes] 409
proteins, diabetic retinitis and, [Sparks] 230
proteins, source of for breakfasts, blood sugar level and, [Coleman & others] 393
reducing, in hypoglycemic patient, [Queries and Minor Notes] 66
use of exchange lists in, [Caso] 472
DIETHYLDITHIOCARBAMATE, damage to *a*-cells of pancreas and, [Wachstein] 68
DIETHYLSTILBESTROL, diabetic pregnancy and, [Hurwitz & Higano] 58
effects on growth of islands of Langerhans, [Kerr & others] 152
effects on hereditary obesity-diabetes syndrome in mice, [Mayer & others] 406
effects on normal force-fed rats, [Ingle] 400
DIGESTION, radiological study of rate of passage of brown and white bread through digestive tract, [McCance & others] 486
DI-INSULIN-NOVO, clinical experiences with, [Kaechele & Petrides] 400
DIMERCAPROL: See BAL
DISABILITY, causes of, in patients with chronic disease, [Goodman] 479
DISEASES, allergic, diabetes and, [Gutmann] 398
vasospastic, caudal analgesia in, [Galley] 397
DIURESIS, stress and, [Hinkle & Wolf] 307
DREYPAK, [Olmsted & others] *37
DRIVING, hypoglycemia and, [Lawrence] 60
DUBLIN, Louis I., retirement, [editorial] *237
DUODENAL ULCER, diabetes and, [Queries and Minor Notes] 228
DUODENOPANCREATECTOMY, papilloma of pancreatic duct and, [Hendry] 58
DUODENUM, aberrant pancreatic tissue in, [Feldman & Weinberg] 148
DWARFISM, hypoglycemia and convulsions with, therapy, [Steiner] 413
pituitary, hereditary, in mice, effects of fasting on blood sugar in, [Mirand & Osborn] 406
with juvenile diabetes, [editorial, Guest] *415
DYSMENORRHEA, membranous, diabetes and, [Treiber & Norton] 314

E

ECK FISTULA, effects, [Hallett & others] 57
ECZEMA: See Skin, diseases
ELECTRIC SHOCK, effects on glucose metabolism, [Altschule & others] 142
ELECTROCARDIOGRAM, effects of heparin on, [Engelberg] 148
hypercalcemia and, [Yu] 234
ELECTROENCEPHALOGRAM, the effect of atropine on, during induced hypoglycemia, [Evarts & others] 477
ELECTROENCEPHALOGRAPHY, in labile diabetes, [Fabrykant] 397
in diabetes mellitus, [Izzo & others] *93
ELECTROLYTES, diabetic coma and, [Duncan] 219
in plasma and erythrocytes, diabetic acidosis and, [Nichols & Nichols] 310
intercapillary glomerulosclerosis and, [Neubauer & Sindoni] 310
renal insufficiency and, [Neubauer & Sindoni] 310
retention in diabetic acidosis, [Darrow & Pratt] 218
EMPLOYMENT OF DIABETICS, [Brandaleone & Friedman] *458
ENDOCRINE GLANDS, diseases, diagnosis, [Soffer] 313
EOSINOPENIA, desoxycorticosterone and, during insulin shock therapy, [Zimmerman & others] 234
EOSINOPHILS, circulating, diabetes and, [Kjems] 225
changes, in response to epinephrine, ACTH and hypoglycemia, in juvenile diabetes, [Grinspoon] 479
count, in insulin hypoglycemia, [Mackenzie Shattock & Micklem] 62
desoxycorticosterone acetate and, during insulin shock therapy, [Zimmerman & others] 234
epinephrine and, in sheep, [Zarrow & others] 234
insulin and, in sheep, [Zarrow & others] 234
EPIDURAL BLOCK, pancreatitis and, [Berk & Krumperman] 144
EPINEPHRINE, changes in eosinophils in juvenile diabetes in response to, [Grinspoon] 479
effects on blood glucose and eosinophils in sheep, [Zarrow & others] 234
effects on carbohydrate metabolism, [Walaas & Walaas] 414
effects on depancreatized dogs, [Foa & others] 149
effects on tissue electrolytes, in normal and demedullated rats, [Dury & Moss] 147
insulin inactivation by, in schizophrenia, [Gottfried & others] 398
pretreatment with, effects, [Dury] 219
ERGOTHIONEINE, in blood, in experimental diabetes, [Beatty] 391
ERYTHROCYTES, electrolytes, in diabetic acidosis, [Nichols & Nichols] 310
water, in diabetic acidosis, [Nichols & Nichols] 310
zinc content of, [Maske & Wolff] 405
ESTERASE, activity, in rabbit bone marrow, [Evans] 305
ESTRADIOL, glycogen deposition in different skeletal muscles induced by, [Leonard] 483
ESTRADIOL BENZOATE, effects on growth of islands of Langerhans, [Kerr & others] 152
ESTROGENS, antidiabetogenic action in experimental diabetes, [Acevado & Migone] 469
diabetes development and, [Lopis & others] 61; [Rodriguez] 311

pancreas endocrine system and, [Rodriguez] 312
ETHYLENEDIAMINE, relationship of the adrenal glands to the diabetogenic effect of, in the partially depancreatized rat, [Ingle and others] 482
ETHER, metabolic effects, [Brewster & others] 216
ETHIONINE, damage to pancreas and, [Wachstein] 68
EXCHANGE LISTS, use in diabetic diet, [Caso] 472
EXTON-ROSE TEST, evaluation, [Womack & Moyer] 70
EYES, asthenopia, extraocular muscle palsies, hordeola, iris changes, and lipemia retinalis in diabetes, [Marks] 485
cataracts caused by carbohydrates, [Patterson] 488
changes, alloxan diabetes and, [Janes & others] 151
changes, blood sugar determination and, [Vere] 315
changes, diabetes and, [Hamilton] *182
changes, diabetes and, [Sacks] 411
damage, microwave irradiation in alloxan diabetes and, [Richardson & others] 66
diabetes and, [Givner] 222; [Heinsius] 223; [Minton] 63; [Peterson] 228
diabetes and, prognosis, [Cordes] 217
diabetic retinafathy, [Murphy] 487
glucose, of the retina, [Kornblueth] 483
ocular changes in diabetes and their effect on the patient's vision, [Cordes] 473
ophthalmological aspects of diabetes, [Marks] 485
reversible diabetic sixth nerve palsy, [Gupta] 480
secondary glaucoma and rubeosis iridis, [Queries and Minor Notes] 488

F

FASTING, blood sugar in hereditary hypopituitary dwarf mice and, [Mirand & Osborn] 406
blood sugar in newborn infant and, [Book Review] 145
effects on cholesterol synthesis by the liver, [Chaikoff & Tomkins] 145
effects on fatty acid and cholesterol formation from C^{14} acetate, [Van Bruggen & others] 314
effects on fatty acid formation from C^{14} acetate, [Lyon & others] 153
realimentation following, stress and, [Wilhelmj & others] 70
FAT, arteriosclerosis and, [Morrison] 227
atrophy: See Insulin, administration, atrophy following
cholesterol absorption in body and, [Kim & Ivy] 224
diet: See Diet, fat
in body, relationship to body water, [Hardy & Drabkin] 57; [Moore & others] 63
metabolic disturbance, tuberculosis in diabetic and, [Cooper & Boucot] 146
metabolism, rabbit marrow cells and, [Evans] 305
phospholipid excretion in feces and, [Kim & Ivy] 224
synthesis, carbohydrate metabolism and, thiamine deficiency in, [Gruber] 57
FATIGUE, insulin hypoglycemia in, [Weitzner] 69
FATTY ACIDS, formation from C^{14} acetate, in fasting rat, [Van Bruggen & others] 314
formation from C^{14} acetate, in rat liver, [Haugaard & Stadie] 399; [Lyon & others] 153
formation from C^{14} acetate, in rat liver, effects of insulin and glucose on, [Masri & others] 405
oxidation, in liver, effects of adrenalectomy and cortisone on, [Lipsett & Moore] 405
FETUS, blood sugar regulation in, [Villee] 315
diabetic, mortality, [Hurd] 307
intrauterine roentgenography in determining age, [Adams & others] 469
prediabetic pregnancy and, [Annotations] 49
FISHLENS PROTEIN EXTRACTS, cataracts and, [Shropshire & others] 67
FLUOROACETATE, effects on pyruvate metabolism, [Busch & Potter] 145
FOLIN, OTTO, biographical note, [Marble] *503
FOLIN-WU METHOD, blood sugar determination by, [Tonks] 232
FOOD AND NUTRITION BOARD, recommended daily dietary allowances, revised 1953, [Pollack] *497
FOOD EXCHANGES, [Behrman] *272; [Caso] *275
FOOD INTAKE, glucostatic mechanism of regulation of, [Mayer] 486
hypothalmic lesions and, [Mayer & others] 226
regulation by small intestine, [Hill & others] 58
relation to arteriovenous glucose differences, metabolic hypoglycemia, [Van Italie & others] 490
FOOT, lesions, in diabetes, management, [Miller] 63
FRIEDREICH'S ATAXIA, with diabetes in sisters, [Ashby & Tweedy] 470
FRUCTOKINASE, effects of acidosis on the metabolism of fructose, [Mackler & Guest] 485
FRUCTOSE, blood sugar and, in insulin-induced experimental hypoglycemia, [Bhattacharya & others] 51
effects of acidosis on the metabolism of, [Mackler & Guest] 485
metabolism by extrahepatic tissues, [Wick, Sherrill & Drury] *465
metabolism, comparison with glucose metabolism, [Bertino & others] 391; [Smith & others] 67, 312
metabolism, effects of stress on, [Drucker & others] 219
metabolism, in diabetic, [Editorial] 54
metabolism, in liver of diabetic and normal subjects, [Craig & others] 146
metabolism, in normal subjects and in patients with decreased glucose tolerance, [Smith & others] 312
FRUCTOSE-1:6-phosphate, spectrophotometric determination, [Slater] 230
utilization and excretion of infused fructose, [Bertino & others] 471

G

GALACTOSE, cataracts and, [Patterson] 488
metabolism, disturbances, [Patz] 408;
GALACTOSEMIA, [Bray & others] 52; [Patz] 408; [Birdsong & Wood] 471
galactosuria and aminoaciduria in, paper chromatographic investigation, [Bickel & Hickmans] 144
therapy, [Patz] 408
GALACTOSURIA, galactosemia and, chromatography in, (Bickel & Hickmans] 144
GALLBLADDER, surgery, diabetes and, [Carbonnell Aguilar] 304
GASTROENTERITIS, in infants and children, blood pyruvic acid in, [Passweg] 64
GIANTISM, observed in study of progeny of alloxan diabetic rats, [Bartelheimer] 471
GIERKE'S DISEASE: See Glycogen, storage disease
GLAUCOMA, [Queries and Minor Notes] 488
diabetes and, [Minton] 63
GLOBIN INSULIN, activity, comparison with NPH insulin, [Beardwood & others] 303
comparison with NPH insulin, [Jackson & others] *365
GLOBIN ZINC INSULIN, brittle diabetes and, [Revell] 155
diabetes and, [Revell] 155
GLOMERULOSCLEROSIS: See Intercapillary glomerulosclerosis
GLUCAGON, content of the pancreas, effect of insulin on, [MacGrath & Snedecor] *443
effect on carbohydrate and corticoid metabolism in normal and diabetic subjects, [Kirtley & others] *345
hyperglycemic and glycosuric effects, in the intact force-fed rat, [Cavallero & Malandra] 473
the hyperglycemic glycogenolytic factor of the pancreas, [De Duve] 474
GLUCIDES: See Carbohydrates
GLUCONEOGENESIS: See Glyconeogenesis
GLUCOSE: See also Blood sugar, 3-Methyl glucose
absorption, cellular, diabetes and, [Lestradet] 404
absorption, intestines and, [Cummins] 146
administration, blood sugar in newborn infant and, [Book Review] 145
blood sugar and, in insulin-induced experimental hypoglycemia, [Bhattacharya & others] 51
cataracts and, [Patterson] 488
degradation of, [Bishop] 471
diabetic coma and, [Duncan] 219
effects on adrenal response to cold exposure, [Sterling & Longwell] 413
effects on blood pyruvic acid, [Amatuzio & others] 49
effects on fatty acid formation, alone and combined with insulin, [Masri & others] 405
effects on fatty acid formation, mechanism, [Lyon & others] 153

effects on plasma amino acids, in hepatectomized and nephrectomized dogs, [Flock & others] 397
femoral arteriovenous, effects of insulin on, [Bell & Burns] 50; [Bell & others] 391
galactose intolerance in galactosemia and, [Patz] 408
in blood, rapid estimation with Galatest reagent, [Guest & Lestradet] *350
in cerebrospinal fluid, determination, [Webb & Isaac] 414
in cerebrospinal fluid, diagnostic value of determination, [Webb & Isaac] 414
in hypertension and obesity, [Drazin] *433
in urine, alloxan diabetes and, [Cohen] 52
infusions, effects on pancreas, [Brown & others] 52
metabolism, acidosis and, [Mackler & others] 62
metabolism, by rat diaphragm, importance of experimental conditions, [Brown & others] 393
metabolism, comparison with fructose metabolism, [Bertino & others] 391
metabolism, comparison with fructose metabolism, in various conditions, [Smith & others] 312
metabolism, comparison with invert sugar metabolism, [Bertino & others] 391; [Smith & others] 67
metabolism, effects of stress on, [Drucker & others] 219
metabolism, in diabetic, [Editorial] 54
mobilization of, by phlorizin in patients with mental disorders, [Altschule & others] 469
mode of action of insulin on the intestinal absorption of, [Lourau] 484
ovarian arteriovenous difference values, in rabbits, [Odeblad & Enhörning] 407
oxidation, effects of β-hydroxybutyric acid on, in insulin-treated, eviscerated rabbits, [Drury & Wick] 147
oxygen consumption and, in denervated and innervated muscle, [Gruber & others] 150
rates of utilization of, in erythrocytes and leucocytes, [Guest & others] 479
renal absorption, effect of desoxycorticosterone glucoside on, [Despopoulos & Kaufman] 53
respiratory quotient and, in denervated and innervated muscle, [Gruber & others] 150
synthesis, in fetus, [Villee] 315
synthesis, in liver, measurement, [Bondy] 392
synthesis, kidneys and, in eviscerated monkey, [Reinecke] 228
synthesis, labeled mannose and, [Cook & Lorber] 393
synthesis, labeled palmitic acid and, [Abraham & Chaikoff] 390; [Abraham & others] 142
synthesis, labeled succinic acid and, [Abraham & Chaikoff] 390
tolerance, effects of adrenal resection and Cushing's syndrome on, [Sprague & others] 313
tolerance, effects of electric shock therapy on, [Altschule & others] 142
tolerance, tests, interpretation, [Amatuzio & others] 390; [Futcher & Sauvé] *31
tolerance, tests, methods and evaluation, [Womack & Moyer] 70
tolerance, tests, pancreatic disease diagnosis and, [Machella] 405
tolerance, tests, pancreatic islet cell adenoma and, [Cant] 304
tolerance, tests, prediabetes and, [Jackson] 59
tubular reabsorption, [Adams] 142
uptake, effects of growth hormone on, in isolated rat diaphragm, [Park & others] 407
utilization and excretion of infused glucose, [Bertino & others] 471
utilization and hunger, [Mayer] 486
utilization, effects of acidosis on, in erythrocytes and leucocytes, [Graubarth & others] 479
GLUCOSE UTILIZATION, effect of hormones on isolated tissue, [Krahl] *26
GLUCOSE-6-PHOSPHATASE, glycogen storage disease and, [Cori & Cori] 393; [Editorials and Comments] 220; [Illingworth & Cori] 400
GLUCOSE-1-PHOSPHATE, in liver, alloxan diabetes and, [Sacks] 411
GLUCOSE-6-PHOSPHATE, in liver, alloxan diabetes and, [Sacks] 411
β-GLUCURONIDASE, in leukocytes, in health and disease, [Follette & others] 306
GLUCOSTATIC MECHANISM of regulation of food intake, [Mayer] 486
GLUTATHIONE, in blood, carbohydrate tolerance and, during ACTH therapy, [Joiner] 59
in blood, in experimental diabetes, [Beatty] 391
potassium tolerance and, in adrenalectomized mice, [Martorano & others] 405
GLYCERIDE GLYCEROL, biosynthesis, mechanism, [Doerschuk] 147
GLYCOGEN, biosynthesis, glucose-6-phosphatase and, [Editorials and Comments] 220
biosynthesis, mechanism, [Doerschuk] 147
changes in tissues in the hamster during arousal from hibernation, [Lyman & Leduc] 84
deposition in different skeletel muscles induced by cortisone and estradiol, [Leonard] 483
deposition of tissues in diabetes, [Warren] *258
human samples, chain length, [Illingworth & Cori] 400; [Polglase & others] 409
human samples, preparation, [Polglase & others] 409
human samples, purity, [Polglase & others] 409
human samples, sedimentation patterns in normals and in patients with glycogen disorder, [Polglase & others] 409
infiltration of tissues in diabetes, [Hamilton] *180
in leukocytes, in health and disease, [Valentine & others] 314
in liver: See Liver, glycogen
in muscle: See Muscle, glycogen
storage disease, [Editorials and Comments] 220
storage disease, glucose-6-phosphatase activity in, [Cori & Cori] 393; [Editorials and Comments] 220
storage disease, liver and muscle glycogen structure in, [Illingworth & Cori] 400; [Polglase & others] 409
storage disease, pathogenesis, [Cori & Cori] 393
structure, determination, [Illingworth & Cori] 400; [Illingworth & others] 400; [Larner & others] 403; [Polglase & others] 409
synthesis, glucose and, [Cook & Lorber] 393
synthesis, labeled mannose and, [Cook & Lorber] 393
GLYCOGENOLYSIS, growth hormone and, [Editorial] 220
hepatic, absence of moderating action of insulin with regard to, [Benard and others] 471
GLYCOGENOLYTIC FACTOR, in insulin, [Audy & Kerly] 143
GLYCONEOGENESIS, adrenocortical steroids and, [Cohn & others] 53; [Kinsell & others] 402
oleic acid and, in cat's liver, [Barford] 390
renal, measurement of, [Bollman & Grindlay] 51
GLYCOSURIA, ACTH-produced, potassium chloride diet and, [Glafkides & others] 56
acute abdomen and, [Khedroo & Di Gilio] 59
cortisone and diethylstilbestrol induced, [Ingle] 400
cortisone-induced, effects of salicylate on, [Smith] 230
effect of aspirin on, in partially depancreatectomized rats, [Ingle & Meeks] 307
functional, as a psychosomatic disorder, [Smolen] 230
GOMORI'S STAIN, demonstration of beta granules in islets of Langerhans with modification of, [Nerenberg] *130
GONADS, islands of Langerhans growth and, [Kerr & others] 152
GOUT, insulin hypoglycemia in, [Weitzner] 69
GROWTH, effects of pancreas hyperglycemic factor on, in hypophysectomized rat, [Elrick] 396
GROWTH HORMONE, carbohydrate metabolism and, [Editorial] 219
diabetogenic action, [Bach & others] 303; [Editorial] 220
diabetogenic action, determination, [Mayer & Silides] 309
diabetogenic action, effects of ACTH on, [Reid] 410
diabetogenic action, relation of growth-promoting activity to, [Reid] 410
effects on blood sugar, in hypophysectomized rats, [Park & others] 407
effects on glucose uptake, in isolated rat diaphragm, [Park & others] 407

effects on hereditary obesity-diabetes syndrome in mice, [Mayer & others] 406
growth-promoting activity, effects of ACTH and thyrotropin on, [Reid] 410
insulin-like action of, [Ottaway] 487
insulin tolerance in adrenalectomized dogs and, [Lazarus & Volk] 224
retention of potassium, sodium, chlorides and nitrogen and, in adrenalectomized rats, [Stein & others] 231
testosterone and, effects on muscle glycogen in hypophysectomized female rats, [Bowman] 392
GROUP THERAPY, of obese diabetics, [Goodman & others] *280

H

HEART, congestive heart failure and diabetic acidosis, [Luikart] 484
disease, coronary, century-old persons and, [Russell] 411
disease, diabetes and, insulin hypoglycemia in, [Chitwood] 304
disease, diabetes and, mortality, [Foreign Letters] 149
disease, mortality, cholesterol consumption and, [Pihl] 64
effects of drugs on, [Bleehen & Fisher] 216
HEMOCHROMATOSIS, the heart in, [editorial, Marble] *72
insulin-resistant diabetes assocated with, [Eskind & others] 477
portal hypertension and, therapy, [Dunlap & others] 54
HEMOPTYSIS, tuberculous diabetics and, [Cooper & Boucot] 146
HEMORRHAGE, gastro-intestinal, diabetes and paramyloidosis and, [Pocock & Dickens] 310
HEPARIN, angina pectoris and, [Engelberg] 148
coronary arteriosclerosis and, [Engelberg] 148
diabetic glomerulosclerosis and, [Engelberg & others] 220
effect on lipoprotein patterns in man, [Loewe & others] 484
peripheral arteriosclerosis and, [Engelberg & Massell] 221
HEPATECTOMY, effects on alkaline phosphate and amylase in plasma, [Flock & others] 148
effects on serum lipoproteins and cholesterol, [Lewis & others] 404
HEPATOLENTICULAR DEGENERATION: See Wilson's disease
HEPATOMEGALY, diabetes and gastro-intestinal hemorrhage and, [Pocock & Dickens] 310
with juvenile diabetes, [editorial, Guest] *415
HEREDITY, diabetes and, [Bleisch & others] 51; [Editorial] 54; [Iannaccone & others] 223
galactosemia and, [Patz] 408
HEXAMETHONIUM, insulin hypoglycemia and, [Laurence & Stacey] 60
HEXOKINASE, in intestines, effects of diet on activity of, [Long] 225
HEXOSEMONOPHOSPHATE, spectrophotometric determination, [Slater] 230
HGF: See also Nesocrine
activity, effects of alkaline on, [Saka] 312
activity, effects of insulin on, [Saka] 312
activity, effects of tryptic digestion on, [Saka] 312
effect on carbohydrate and corticoid metabolism in normal and diabetic subjects [Kirtley & others] *345
effects on depancreatized dogs, [Foà & others] 149
effects on man, [Kibler & others] 401
hyperglycenic and glycosuric effects in intact force-fed rat, [Cavallero & Malandra] 473
in blood, in diabetic man and alloxan-diabetic animals, [Saka] 312
in urine, in diabetic man and alloxan-diabetic animals, [Saka] 312
secretion, in normal dogs, [Foà & others] 221
HISTAMINE, gastric secretion induced by, effects of insulin hypoglycemia on, [Karvinen & Karvinen] 401
HISTORY OF DIABETES MELLITUS, book review, [Reviews] 66
HORMONES, diabetic pregnancy and, [Jones] 223
retinal blood vessels and, [Heinsius] 223
HOSPITAL, for diabetics, [Editorial] 305
HOUSSAY ANIMAL, [editorial, Lukens] *491
HOUSSAY PHENOMENON IN MAN, [Poulsen] *7
HYALURONIDASE, effect on rectal insulin absorption, [Klotzbucher] 59
insulin aerosol administration and, [Knick & Wehr] 402
HYDERGINE, peripheral vascular disease and, [Roberts & others] 228
HYDRATION, diabetic coma and, [Duncan] 219
β-HYDROXYBUTYRIC ACID, determination, [Thin & Robertson] 314
effects on glucose oxidation in insulin-treated, eviscerated rabbits, [Drury & Wick] 147
8-HYDROXYQUINOLINE, diabetes production by destruction of β-cells of islands of Langerhans with, [Wachstein] 68
HYPERCALCEMIA, electrocardiographic changes in, [Yu] 234
HYPERGLYCEMIA: See also Blood sugar
acute abdomen and, [Khedroo & Di Gilio] 59
alloxan and, in rhesus monkeys, [Ramfjord] 228
blood phosphorus levels in various types, [Queries and Minor Notes] 311
cortisone-induced, effects of salicylate on, [Smith] 230
cortisone-induced, glucose production in, [Stetten] 313
diabetes and, carbohydrate tolerance and, [John] 59
disappearance of, following estrogen therapy in experimental diabetes, [Acevado & Migone] 469
effects of aspirin on, in partially depancreatectomized rats, [Ingle & Meeks] 308
effects on transfer of glucose from liver to blood stream, [Searle & Chaikoff] 158
ether anesthesia and, [Brewster & others] 216
functional, as a psychosomatic disorder, [Smolen] 230
glycogenolytic factor: See HGF
HGF-induced, in man, [Kibler & others] 401
isocaloric diet and, [Anderson] 470
relationship to hyperlipemia in diabetics, [Hirsch & others] 307
HYPERGLYCEMIC FACTOR, in pancreas, [Pincus] 65
in pancreas, growth effects in hypophysectomized rat, [Elrick] 396
HYPERINSULINISM, functional, as a psychosomatic disorder, [Smolen] 230
islet cell tumor with surgical cure, [Pickard & others] 488
pancreatic adenomas and, [Luisi] 61; [Osnes & Thorsen] 407; [Pickard & others] 408
pancreatic tumors and, [Waugh] 69
surgery in, [Hellstrom] 223
HYPERLIPEMIA, diabetic acidosis and, [Harris & others] 306
essential, [Joyner] 400
relationship to hyperglycemia in diabetics, [Hirsch & others] 307
HYPERPHAGIA, hypothalamic, hyperthermia in, [Mayer] 486
HYPERTENSION, frequency in diabetics, [Bell] *377
HYPERTENSION AND OBESITY, glucose tolerance in, [Drazin] *433
HYPERTHERMIA, in hypothalamic hyperphagia [Mayer] 486
HYPERTHYROIDISM, as a psychosomatic disorder, [Smolen] 230
HYPOCALCEMIA, electrocardiographic changes in, [Yu] 234
HYPOCHLOREMIA, in infants and children, blood pyruvic acid in, [Passweg] 64
HYPOGLYCEMIA: See also Blood sugar; Insulin, hypoglycemia
automobile accidents and, [Lawrence] 60
changes in eosinophils in juvenile diabetes in response to, [Grinspoon] 479
coma, pancreatic adenoma and, [Luisi] 61
diet in, [Queries and Minor Notes] 66
dwarfism and, [Steiner] 413
effect of atropine on electroencephalogram during, [Evarts & others] 477
fatal, in a diabetic patient with pituitary necrosis, [Alexander] 469
gastric acid and, [Levy & others] 60
hepatic, mechanism, [Editorial] 220
insulin-induced, effects of injections of glucose, fructose and invert sugar on blood sugar level in, [Bhattacharya & others] 51
manifestations and their relation to blood sugar levels, [Revitch] 489
neurogenic, therapy, [Queries and Minor Notes] 409
night sweats, [Queries and Minor Notes] 488
pancreatic tumors and, [Waugh] 69
reaction to long-acting insulins, [Maddock & Krall] 485
relation to arteriovenous glucose dif-

ferences and food intake, [Van Italie & others] 490
stomach resection and, [Medical Literature Abstracts] 309
HYPOPHYSECTOMY, cholesterol synthesis in liver and, [Tomkins & others] 414
fasting ketosis and, [Bahner & Taylor] 471
insulin sensitivity and, [de Bodo & others] 146
insulin sensitivity and, effects of adrenocortical steroids on, [de Bodo & others] 147, 394
HYPOPITUITARISM, with diabetes, [Poulsen] *7
HYPOPLASIA, in exocrine tissue of pancreas, [Lumb & Beautyman] 226
HYPOTHALAMUS: See Brain

I

IMPOTENCE, diabetes and, [Queries and Minor Notes] 155; [Schept] 229
INANITION, in infants and children, blood pyruvic acid in, [Passweg] 64
INDUSTRIAL MEDICINE, diabetes in, [Brandaleone & Friedman] *448
INFANTS, care of, of a diabetic mother, [Queries and Minor Notes—Bolinske] 488
newborn, blood sugar in, [Book Review] 145; [Creery & Parkinson] 394
newborn, diabetes and, [Parmelee] 154
of diabetics, care, [Heck] 222
INFECTIONS, diabetes and, management, [John] 152
INFLUENZA, in infants and children, blood pyruvic acid in, [Passweg] 64
INJURY, metabolic response to, effects of cortisone on, [Engel & Burns] 396
ISLET CELL TUMOR of the pancreas, with surgical cure, [Pickard & others] 488
INSULIN, absence of moderating action on hepatic glycogenolysis, [Benard & others] 471
absorption, following injection into femoral artery, [Bell & others] 391
absorption, following injection into femoral artery and antecubital vein, [Bell & Burns] 50
absorption, rectal administration preceded by hyaluronidase, [Klotzbucher] 59
action, [Stetten] 313
action, acidosis and, [Mackler & others] 62
action, hexamethonium and, [Laurence & Stacey] 60
action on transfer of sugars across cell barriers; common chemical configuration of substances responsive to action of the hormone, [Goldstein & others] 478
action, surviving rat's heart and, [Bleehen & Fisher] 216
administration, aerosol method, [Knick & Wehr] 402
administration, atrophy following, [Queries and Minor Notes] 310
administration, rectal, absorption, [Klotzbucher] 59
allergy, denatured insulin and, [Dolger] 395
allergy, failure of denatured insulin in prevention of, [Hollander & Zinn] 481
allergy to, [Queries and Minor Notes—Dolger] 489
allergy treated by Chlor-trimeton, [Queries and Minor Notes—Dolger] 489
comparison of Globin and NPH insulin, [Jackson & others] *365
comparison with action of muscular work in transfer of sugars across cell barriers, [Goldstein & others] 478
concentration in Protamine Zinc Insulin, [Robinson & Fehr] 66
cortisone antagonism and, [Stetten] 313
denatured, failure of, in the prevention of urticaria caused by insulin, [Hollander & Zinn] 481
denatured, in insulin allergy, [Dolger] 395
denatured, in treatment of allergy to insulin, [Queries and Minor Notes—Dolger] 489
derivatives, of thiocarbamyl, [Kaiser & others] 224
diabetes and, coma, [Duncan] 219; [Stephens & Root] 413
diabetes and, gallbladder surgery in, [Carbonnell Aguilar] 304
diet and, [Greenhouse] 57
dosage, [Delore] 147
dosage, adrenal cortical activity and, [McArthur & others] 62
dosage, in tubercular diabetic, effect of isonicotinic acid hydrazide on, [Spiegelman & Quicgley] 313
effects on blood glucose and eosinophils in sheep, [Zarrow & others] 234
effects on blood glucose, in rats with hypothalamic lesions and normals, [Beattie & Chambers] 390
effects on blood pyruvic acid, [Amatuzio & others] 49
effects on cataract development in diabetic rats, [Patterson] 408
effects on cholesterol synthesis, in diabetic liver, [Hotta & Chaikoff] 399
effects on depancreatized dogs, [Foà & others] 149
effects on fatty acid formation from C^{14} acetate, alone and combined with glucose, [Masri & others] 405
effects on femoral arteriovenous glucose difference, [Bell & Burns] 50; [Bell & others] 391
effects on glucose metabolism in ascorbic acid deficiency and scurvy, [Stewart & others] 231
effects on liver in normal and diabetic subjects, [Annotations] 142; [Bearn & others] 303
effect on metabolism of isolated tissue, [Krahl] *26
effects on regeneration of liver phosphatase after lobectomy, [Norberg] 154
effects on serum citric acid, in schizophrenia, [Gottfried & others] 398
effects on tissue electrolytes, in normal and demedullated rats, [Dury & Moss] 147
effects on urinary excretion of 17-ketosteroids in alloxan-diabetic rabbits, [Koref & Errazuriz] 308
fibrous, electron microscopical observations of, [Farrant & Mercer] 55
gastric acid and, [Levy & others] 60
glucose and, tolerance test, diabetes diagnosis and, [Volk & Lazarus] 315
glucose and, tolerance test, effect of insulin dose on blood sugar decline rate, [Volk & Lazarus] 414
glucose and, tolerance test, pituitary gland disease diagnosis and, [Sofer] 313
glycogenolytic factor content of, [Audy & Kerly] 143
glycogenolytic factor content of, statistical examination of multiple-dose assays, [Please] 155
HGF activity and, [Saka] 312
hypersensitivity: See Insulin, sensitivity
hypoglycemia, allergy and, [Weitzner] 70
hypoglycemia, diabetes and, effects on heart, [Chitwood] 304
hypoglycemia, effects in various conditions, [Weitzner] 69
hypoglycemia, effects on histamine-induced gastric secretion, in dogs, [Karvinen & Karvinen] 401
hypoglycemia, eosinophil count in, [Mackenzie Shattock & Micklem] 62
hypoglycemia, gout and, [Weitzner] 69
hypoglycemia, hexamethonium and, [Laurence & Stacey] 60
hypoglycemia, in treatment of rheumatoid arthritis of menopausal women, [Godlowski & Paterson] 56
hypoglycemia, narcolepsy and, [Weitzner] 69
hypoglycemia, rheumatoid arthritis and, [Weitzner & Snowden] 69
hypoglycemia, skin diseasees and, [Weitzner] 69, 70
inactivation by deuterons and electrons, [Setlow & Doyle] 229
influence of ascorbic acid on carbohydrate metabolism in adrenalectomized and adrenaldemedullated rats studied by insulin tolerance tests, [Bacchus & Heiffer] 470
influence on protein metabolism, [editorial, Lukens] *491
in plasma, in diabetes, [Bornstein] 472
lente: See also Insulin, long-acting
lente, [Lawrence & Oakley] 403
Lipodystrophy a study of 14 cases, [Boulin & others] 472
long-acting: See also Insulin, lente
long-acting, [Editorial] 396; [Lawrence & Oakley] 403; [Hallas-Moller & others] 398
manufacture and distribution, in Argentina, [Foreign Letters] 55
manufacture and distribution, in British Empire, [Annotations] 143; [Foreign Letters] 306
mode of action on the intestinal absorption of glucose, [Lourau] 484
modifications, Di-Insulin-Novo, [Kaechele & Petrides] 400
modifications, globin insulin, [Beardwood & others] 303
modifications, globin zinc insulin, [Revell] 155
modifications, lente insulin, [Lawrence & Oakley] 403

modifications, NPH insulin, [Beardwood & others] 303; [Carbonnell Aguilar] 304; [Essellier & others] 396; [Lacey] 60; [Reaud] 410; [Ricketts] 156
modifications, protamine zinc insulin, [Editorial] 396; [Nerenberg] 407; [Reaud] 410; [Robinson & Fehr] 66; [Spiegelman & Quicgley] 313
modifications, zinc insulin, [Hallas-Moller & others] 398
molecular weight, [Creeth] 53, 218; [Editorials and Comments] 305; [Setlow & Doyle] 229
molecule, structure, [Editorials and Comments] 305; [Wrinch] 233
new modified type, study of, [Mukherjee] 486
obesity and age relationship to, in a diabetes clinic, [Oppenheimer] 487
overdosage, [Delore] 147
physiology, [Bruch] 217
pretreatment with, effects, [Dury] 219
pseudohypoglycemic reactions, hyperventilation and, in diabetes, [Musser & others] 487
reactions; manifestations and need for recognition of long-acting insulin reactions, [Maddock & Krall] 485
reactions, night sweats, [Queries and Minor Notes] 488
recrystallized, in insulin allergy, [Ljung] 61
resistance, [editorial, Lukens] *160
resistance, [Loveless & Cann] 225
resistance, after administration of ACTH and cortisone, [Kinsell & others] 402
resistance, denatured insulin and, [Dolger] 395
resistance, diabetes and associated with interstitial cell tumor of the testis, [Lopis & others] 61
resistance, familial diabetes and, [Bleisch & others] 51
resistance from antibody formation, [Rausch-Strooman & Sauer] 489
resistance, hereditary obesity-diabetes syndrome in mice and, [Mayer] 406; [Mayer & others] 406
resistance, in diabetic coma, [Rose, Kaplan & Picard] *462
resistance, recrystallized insulin and, [Ljung] 61
resistance, steriod hormone-induced, relationship of potassium to, [Kinsell] 482
resistance, temporary, diabetic acidosis and, [Robillard] 411
response, variability of, in rabbits, [Feinblatt & Ferguson] 55
reversible association processes, [Steiner] 231
sensitivity, adrenalectomized dog and, [de Bodo & others] 146
sensitivity, effects of diabetic plasma on, [Bornstein] 52
sensitivity, in hypophysectomized dogs, [de Bodo & others] 146, 147, 394
sensitivity, in hypophysectomized dogs, effects of adrenocortical steroids on, [de Bodo & others] 147, 394
shock, gastric acidity and, [Levy & others] 60
shock, schizophrenia and, [Morrow & others] 154
shock, schizophrenia and, intravenous injection in, [Evseeff] 148
shock, therapeutic use of, blood cholesterol level during, in schizophrenia, [Goodman & Kanter] 56
shock, therapeutic use of, in desoxycorticosterone acetate pre-treated patients, [Zimmerman & others] 234
structure, [Wrinch] 233
studies of radioactive preparations, [Elgee & others] *370
susceptibility to, after total pancreatectomy in man, [Honjo & Araki] 481
therapy, fatal complication following, in rheumatoid arthritis, [Simpson & Trowbridge] 490
tolerance in schizophrenia, [Nadeau & Rouleau] 487
tolerance, pituitary growth hormone and, [Lazarus & Volk] 224
tolerance, tests, in pituitary and thyroid disease, [Aziz & Bebawi] 144
two new types of long-acting preparations, [Izzo & others] *358
uptake of amino acids by tissue and, [Krahl] 224
INSULOMA: See Pancreas, islands of Langerhans, adenoma
INTERCAPILLARY GLOMERULOSCLEROSIS, [Bell] *379
diabetes and, [Loomis] 405; [Robbins & others] 156; [Rogers & Robbins] 157
diabetes and, diagnosis, [Rogers & others] 157
diabetes and, etiology, [Hall] 150
diabetes and, serum lipids and lipoproteins in, [Engelberg & others] 220
diabetic retinopathy and, [Agatston] 215
electrolytes in, [Neubauer & Sindoni] 310
sodium lactate in, [Neubauer & Sindoni] 310
INTERNATIONAL DIABETES FEDERATION, [Lawrence] 403
INTESTINES, glucose absorption and, [Cummins] 146
hexokinase activity of, effects of diet on, [Long] 225
methionine absorption and, [Cummins] 146
regulation of food intake and, [Hill & others] 58
INTRAVENOUS THERAPY of isotonic glucose or saline solutions with citrated blood, simultaneous administration, [Queries and Minor Notes—Gifford] 489
INVERT SUGAR, utilization and excretion of infused invert sugar, [Bertino & others] 471
IODINE, protein-bound, in normal and diabetic children, [Danowski & others] 53
IONS, in plasma, effects of intravenous glucose after pretreatment with insulin or epinephrine, [Dury] 219
IRRADIATION, microwave, ocular damage in alloxan diabetes and, [Richardson & others] 66
x-ray, effects on liver glycogen, [Levy & Rugh] 308
ISLANDS OF LANGERHANS, [Lukens] *161
demonstration by Laguesse, [Hoet] *322
demonstration of beta granules with modification of Gomori's stain, [Nerenberg] *130
effects of anterior pituitary extracts and growth hormone preparations on, [Haist & others] *112
factors affecting, [Haist] *295
lesions in diabetics, [Warren] *257
ISONIAZID, carbohydrate metabolism disturbance and, [Evans & Stradling] 396
diabetes and, [Correspondence] 394
nitrogen metabolism and food intake in nontuberculous patients during treatment, [Faloon] 477
tubercular diabetic and, [Spiegelman & Quicgley] 313
ISONICOTINIC ACID HYDRAZIDE: See Isoniazid
ISOPROPYL ALCOHOL, determination, [Thin & Robertson] 314

J

JUVENILE DIABETES, [Chute] *268
changes in eosinophils, in response to epinephrine, ACTH and hypoglycemia, [Grinspoon] 479
isocaloric diet in management, [Anderson] 470
management of, [Chute] *268
serum cholesterol in, [Dine & Jackson] *206
the Mauriac syndrome, [editorial, Guest] *415

K

KAPOSI'S SARCOMA, diabetes and, [Ronchese & Kern] 312
a-KETOGLUTARATE, oxidation, influence of thioctic acid on, [Seaman] 312
KETONE BODIES, determination, [Thin & Robertson] 314
in blood, diabetic coma and, [Duncan] 219
in blood, stress and, [Hinkle & Wolf] 307
in urine, effects of niacin on, [Janes & Boeke] 151
in urine, effects of priscoline on, [Janes & Boeke] 151
in urine, effects of sodium gluconate on, [Koster] 402
in urine, stimulants in horse meat extracts, [Stewart & Young] 231
KETONURIA: See Ketone bodies, in urine
KETOSIS, clinical features, [McCullagh] *171
fasting, in hypophysectomized and normal rats, [Bahner & Taylor] 471
17-KETOSTEROIDS, excretion, in alloxan-diabetic rabbits, [Koref & Errazuriz] 308
KIDNEYS: See also Arteriosclerosis, Renal; Glycosuria; Intercapillary glomerulosclerosis; Necrosis; Nephrectomy; Nephrosis; Pyelonephritis; Tubular reabsorption; Urinary tract; Urine

alloxan and, in rhesus monkeys, [Ramfjord] 228
carbohydrate metabolism and, [Dratz & Handler] 395
changes in diabetes, [Hamilton] *182
pathologic changes in diabetes, [Warren] *258
diseases, diabetes and, [Loomis] 405; [Review] 410
diseases, diabetes and, mortality, [Foreign Letters] 149
renal vascular disease in diabetes, [Bell] *376
glomeruli, diseases affecting, retinopathy and, [Gartner] 306
glucose synthesis and, in eviscerated monkey, [Reinecke] 228
glyconeogenesis, measurement of, [Bollman & Grindlay] 51
insufficiency, electrolyte therapy in, [Neubauer & Sindoni] 310
pedicles of, effects of clamping in alloxan diabetic dogs, mechanism, [Arteta] 50
phosphate metabolism and, [Dratz & Handler] 395
physiology, diabetic coma and, [Bernstein & others] 51
physiology, intercapillary glomerulosclerosis and, [Agatston] 215
KIMMELSTIEL-WILSON syndrome: See Intercapillary glomerulosclerosis

L

LABORATORY PROCEDURE, errors in, [Henry & Berkman] 481
LACTOSE, in urine, burn therapy and, [Baar & Bull] 302
LAGUESSE, Edouard Gustave, biographical note, [Hoet] *322
LEIOMYOSARCOMA, retroperitoneal, metabolism following pancreatectomy in, [Nardi] 64
LENS, changes in, diabetes and, [Peterson] 228; [Sacks] 411
metabolism, carbohydrates and, [Nordman & Mandel] 407
LENTE INSULIN: See Insulin, lente
LEUKOCYTES, β-glucuronidase content, in health and disease, [Follette & others] 306
glycogen content, alkaline phosphatase activity and, [Valentine & others] 314
glycogen content, in health and disease, [Valentine & others] 314
LIPASE, in serum, pancreatectomy and, [Nardi] 64
LIPEMIA RETINALIS, diabetes and, [Nadbath & Fauteux] 64
nondiabetic, etiology, [Everett] 221
LIPIDS, deposition, arteriosclerosis and, [Gofman] 56
in aorta, effects of adenosine-5-monophosphate on, [Milch & others] 153
in blood, diabetics with arteriosclerosis and, [Dewind & others] 395; [Hirsch & others] 307
in coronary arteries, analysis of, in normal and diabetic arteries, [Lundbaek & Petersen] 309
in serum in relation to atherosclerosis, [editorial, Ricketts] *316
in serum, diabetic acidosis and, [Harris & others] 306
in serum, diabetic glomerulosclerosis and, [Engelberg & others] 220
in serum, effects of adenosine-5-monophosphate on, [Milch & others] 153
metabolism, disorder, arteriosclerosis and, [Hatch] 150
LIPODYSTROPHY, from insulin, a study of 14 cases, [Boulin & others] 472
lipo-atrophy and, differences between, [Lawrence] 225
LIPOGENESIS: See Fatty acids
LIPOPROTEINS, effect of heparin on, [Loewe & others] 484
in serum, determination, in normal and diabetic subjects, [Kempe & others] 401
in serum, determination, in normal, hypertensive and hypothyroid animals, [Lewis & others] 308
in serum, diabetic glomerulosclerosis and, [Engelberg & others] 220
in serum, effects of hepatectomy on, [Lewis & others] 404
LIPOTROPIC FACTOR, of pancreas, development of diabetic retinopathy and, [Givner] 222
LITHIASIS, pancreatic, pancreatic cysts within, [Alexander & Lowder] 49
LIVER: See also Hepatectomy, Hepatomegaly
alloxan and, in rhesus monkeys, [Ramfjord] 228
blood circulation, effects of Eck fistula on, [Hallett & others] 57
blood circulation, effects of splenectomy on, [Hallett & others] 57
cholesterol synthesis in, [Chaikoff & Tomkins] 145; [Hotta & Chaikoff] 399; [Werthessen & Schwenk] 233
cirrhosis: See also Wilson's disease
diseases, carbohydrate disturbances in, [Leevy & others] 225
diseases, diabetes with, brucellosis as possible cause of, [Leon & Aguirre] 404
hepatomegaly with juvenile diabetes, [editorial, Guest] *415
effects of insulin on, [Annotations] 142; [Bearn & others] 303
fat, lipotropic action of choline and, [Elvehjem] 220
fatty acid oxidation in, effects of adrenalectomy and cortisone on, [Lipsett & Moore] 405
fetal, glucose production and, [Villee] 315
fructose metabolism and, [Craig & others] 146
glucose, synthesis, effects of Eck fistula on, [Hallett & others] 57
glucose, synthesis, measurement, [Bondy] 392
glycogen, effects of intravenous infusions of potassium on, [Seibert & others] 158
glycogen, effects of niacin on, [Janes & Boeke] 151
glycogen, effects of priscoline on, [Janes & Boeke] 151
glycogen, effects of x-radiation on [Levy & Rugh] 308
glycogen, measurement, [Kibler & others] 401
glycogen, relation to fatty acid synthesis, [Haugaard & Stadie] 399
glycogen, structure, determination, [Illingworth & Cori] 400; [Illingworth & others] 400; [Larner & others] 403; [Polglase & others] 409
hypoglycemia and, mechanism, [Editorial] 220
lipids, effects of niacin on, [Janes & Boeke] 151
lipids, effects of priscoline on, [Janes & Boeke] 151
phosphate, alloxan diabetes and, [Sacks] 411
physiology, surgical patient and, [Child & Payne] 145
water and ionic content, effects of intravenous glucose after pretreatment with insulin or epinephrine, [Dury] 219
LIVER EXTRACTS, diabetic neuropathy and, [Queries and Minor Notes] 155
osteoarthritis and, [Queries and Minor Notes] 155
LOWER NEPHRON SYNDROME with acute necrotizing pancreatitis following transurethral prostatic resection, [Wilkey & others] 490
LUMBAR SYMPATHETIC BLOCK, and LUMBAR SYMPATHECTOMY, in diabetic surgery, [Azar] 470
LUNGS, tuberculosis, amithiozone in, carbohydrate metabolism disturbance and, [Escovitz] 148
LUSK, GRAHAM, biographical note, [Striker] *242
LYMPHOCYTES, count, insulin-glucose tolerance test and, in diabetes diagnosis, [Volk & Lazarus] 315

M

MALNUTRITION, effects on growth of islands of Langerhans, [Ashworth & others] 143
MANNITOL, as sugar substitute, [Olmsted] *132
MANNOSE, labeled, conversion to glucose, [Cook & Lorber] 393
MAST CELLS, relation to susceptibility to experimental atherosclerosis, [Constantinides] 473
MAURIAC SYNDROME, dwarfism, hepatomegaly and obesity with juvenile diabetes mellitus, [editorial, Guest] *415
MEMBERS, newly elected, *169, *255, *342, *429, 510
MENOPAUSE, rheumatoid arthritis and, insulin hypoglycemia in treatment of, [Godlowski & Paterson] 56
MENTAL DISEASES, diabetic management and, [Ross & Gibson] 67
METABOLISM, diabetes and, [Allen] 215
effect of pancreatectomy for retroperitoneal leiomyosarcoma on, [Nardi] 154
METHIONINE, absorption, intestines and, [Cummins] 146
3-METHYL GLUCOSE, metabolism, [Campbell & Young] 145
MONTMORILLONITE, absorption of serum lipids and, [Nikkilä & Oker-Blom] 227

MORTALITY IN OLDER PERSONS, [editorial, Marks] *71
MUCOPOLYSACCHARIDES, changes in diabetes, [Hamilton] *181
MUSCLE, atrophy, diabetes and, [Hirson] 399
glycogen deposition in, induced by cortisone and estradiol, [Leonard] 483
glycogen, effects of testosterone and growth hormone on, in hypophysectomized female rats, [Bowman] 392
glycogen, structure, determination, [Illingworth & Cori] 400; [Larner & others] 403; [Polglase & others] 409
water and ionic content, effects of intravenous glucose after pretreatment with insulin or epinephrine, [Dury] 219
MUSCULAR WORK, action of and comparison with insulin in transfer of sugars across cell barriers, [Goldstein & others] 478
MYELOPATHY, diabetic, [Garland & Taverner] 478
MYOCARDIAL INFARCTION and diabetic acidosis, [Luikart] 484

N

NARCOLEPSY, insulin hypoglycemia in, [Weitzner] 69
NECROBIOSIS LIPOIDICA, [Queries and Minor Notes] 488
NECROSIS, fat, cancer of pancreas and, [Jackson & others] 151
renal medullary, diagnosis, [Review] 410
renal medullary, therapy, [Review] 410
renal papillary, diabetes and, [Keerberghen & Lederer] 401; [Silberstein & Paugh] 412
renal papillary, pathology, [Silberstein & Paugh] 412
NEOGLUCOGENESIS: See Glyconeogenesis
NEPHRECTOMY, alloxan diabetes and, [De Oya & others] 304
NEPHROSIS, classification of various types, [Kimmelsteil] 402
diabetes and, [Loomis] 405
diabetes and, incidence, control of, [Bortz] 304
NERVOUS SYSTEM, diabetes and, [Brousseau] 392
NESOCRINE, hereditary obesity-diabetes syndrome in mice and, [Mayer] 406
NEURITIS, diabetic, [Darrow & Pratt] 218
diabetic, BAL in, [Sparks] 230
retrobulbar, diabetes and, [Givner] 222
NEUROPATHY, diabetic, [Fortuin & Wassing] 55; [Hirson & others] 481
bladder dysfunction, [Spring & Hymes] *199
diabetic, caudal analgesia in, [Galley] 397
diabetic, diabetes diagnosis and, [Davidson] 218
diabetic, extract of pregnant mammalian liver in, [Queries and Minor Notes] 155
diabetic, psychological factors in, [Fortuin & Wassing] 56
diabetic, pupillary changes in, [Pryor] 65
diabetic, therapy, [Brousseau] 392
peripheral, protein content of cerebrospinal fluid in, [Madonick & Magolis] 226
NIACIN: See Nicotinic acid
NICOTINIC ACID, effects on cataract formation in alloxan diabetic rat, [Janes & others] 151
effects on ketonuria, liver glycogen and liver lipids, [Janes & Boeke] 151
NIGHT CRAMPS, in arteriosclerosis obliterans, therapy, [Texter & others] 232
NIGHT SWEATS, [Queries and Minor Notes] 488
NITROGEN, retention, growth hormone and, in adrenalectomized rats, [Stein & others] 231
NOCTURNAL CRAMPS, diabetes and, [Shuman] 229
NORADRENALINE: See Norepinephrine
NOREPINEPHRINE, effects on carbohydrate metabolism, [Walaas & Walaas] 414
NPH INSULIN, activity, comparison of six preparations of, [Lacey] 60
activity, comparison with globin insulin, [Beardwood & others] 303
comparison with globin insulin, (Jackson & others) *365
diabetes and, [Carbonnell Aguilar] 304; [Essellier & others] 396; [Ricketts] 156
tubercular diabetics and, [Reaud] 410
NUTRITION, diabetes and, [Geiger] 150
research, in United States, [Sebrell] 412
NYDRAZID: See Isoniazid

O

OBESITY, decreased activity and energy balance in the hereditary obesity-diabetes syndrome of mice, [Mayer] 486
diabetes and, [Bleisch & others] 51; [Bohan & others] 392; [Editorial] 54
OBESITY, diabetes and, [Richardson] 454; [Duncan] 476
diabetes and, in elderly patients, [Schwartz & Goodman] 158
diabetes and, mortality, [Sebrell] 412
disease mortality and, [Sebrell] 412
food intake and, [Beaudoin & Mayer] 216
group method of weight reduction, [Harvey & Simmons] 480
group therapy of obese diabetics, [Goodman & others] *280
heart disease and, [Editorial] 54
hyperthermia, in hypothalamic syndrome, [Mayer] 486
in juvenile diabetes in the Mauriac syndrome, [editorial, Guest] *415
prediabetes and, pregnancy, [Futcher & Long] 222
pregnancy and, [Richardson] 66
relation to insulin, in a diabetes clinic, [Oppenheimer] 487
OBESITY-DIABETES SYNDROME, hereditary, in mice, decreased activity and energy balance in, [Mayer] 486
hereditary, in mice, acetate metabolism blocking in, [Guggenheim & Mayer] 398
hereditary, in mice, endocrine studies of, [Mayer & others] 406
hereditary, in mice, etiology, [Mayer] 406
hereditary, in mice, metabolic studies of, [Guggenheim & Mayer] 398; [Mayer & others] 406
hereditary, in mice, nesocrine and, [Mayer] 406
hereditary, in mice, nutritional studies of, [Mayer & others] 406
hereditary, in mice, pyruvate metabolism blocking in, [Guggenheim & Mayer] 398
OBESITY AND HYPERTENSION glucose tolerance in, [Drazin] *433
OLEIC ACID, glyconeogenesis in cat's liver and, [Barford] 390
OPHTHALMOSCOPE, for blood sugar determinations, [Correspondence] 394; [Vere] 314
OSTEOARTHRITIS, extract of pregnant mammalian liver in, [Queries and Minor Notes] 155
OVARIES, glucose arteriovenous difference values, in rabbits, [Odeblad & Enhörning] 407
OXYGEN, consumption, effects of glucose on, in denervated and innervated muscle, [Gruber & others] 150
in blood, tension, effects on normal and diseased retinal vessels, [Sieker & Hickam] 412

P

PAIN, in pancreatitis, therapy, [Berk & Krumperman] 144
PALMITIC ACID, labeled, conversion to glucose, [Abraham & Chaikoff] 390; [Abraham & others] 142
PANCREAS, aberrant tissue of, in duodenum, [Feldman & Weinberg] 148
aberrant tissue in the wall of stomach, [Majer] 485
acute necrotizing pancreatitis and lower nephron syndrome following transurethral prostatic resection, [Wilkey & others] 490
alloxan and, in rhesus monkeys, [Ramfjord] 228
calcification: See Lithiasis, pancreatic
cancer, [Alvarez] 49
cancer, diabetes and, [Pirart & Desneux] 65
cancer, diagnosis, [Jackson & others] 151
cancer, fat necrosis in tissue and bone marrow in, [Jackson & others] 151
comparison of clinical and laboratory findings of carcinoma of the pancreas and chronic pancreatitis, [Knight & Muether] 483
constancy of ratio of amylase to protein nitrogen concentration, [Guth & others] 480
cysts, calcified pancreas and, [Alexander & Lowder] 49
demonstration of beta granules in islets with modification of Gomori's stain, [Nerenberg] *130

demonstration of islands by Laguesse, [Hoet] *322
diseases, diabetes and, [Twiss & Carter] 233
diseases, diagnosis, [Machella] 405
duct of Wirsung, papilloma, [Hendry] 58
effects of anterior pituitary extracts and growth hormone preparations on, [Haist & others] *112
effects of insulin on glucagon content in normal and insulin-resistant mice, [MacGrath & Snedecor] *443
factors affecting islets, [Haist] *295
lesions in diabetes, [Hamilton] *180
effects of estrogens on, [Rodriguez] 312
effects of glucose infusion on, [Brown & others] 52
effects of prolonged administration of radioactive Zn^{65} on, [Sherrill & Wick] 312
exocrine function of, [Picard] 408
exocrine tissue of, hypoplasia and, [Lumb & Beautyman] 226
HGF in, [Foà & others] 221; [Saka] 312
glucagon: the hyperglycemic glycogenolytic factor of, [De Duve] 474
hyperglycemic factor, [Pincus] 65
hyperglycemic factor, growth effects in hypophysectomized rat, [Elrick] 396
islands of Langerhans, adenoma, [Cant] 304
islands of Langerhans, adenoma, alloxan and, [Bottger & others] 216
islands of Langerhans, adenoma, cortisone and ACTH in, [Osnes & Thorsen] 407
islands of Langerhans, adenoma, hypoglycemic coma and, [Luisi] 61
islands of Langerhans, adenoma, surgery in, [Bottger & others] 216; [Cant] 304; [Osnes & Thorsen] 407; [Pickard & others] 408
islands of Langerhans, *a*-cells, cholesterol metabolism and, [Francisco] 56
islands of Langerhans, *a*-cells, degeneration by synthalin A, [Davis] 219
islands of Langerhans, *a*-cells, hormone nesocrine of, [Mayer] 406
islands of Langerhans, β-cells, destruction by various agents with subsequent production of diabetes, [Wachstein] 68
islands of Langerhans, β-cells, granules, effects of insulin and starvation on, [Nerenberg] 407
islands of Langerhans, growth, effects of gonads on, [Kerr & others] 152
islands of Langerhans, growth, undernutrition and [Ashworth & others] 143
islands of Langerhans, histology, in normal and diabetic subjects, [Kodousek & Endrys] 402
islands of Langerhans, hyperplasia, familial diabetes and, [Bleisch & others] 51
islands of Langerhans, tumors, [Waugh] 69
physiology, [Picard] 408
phototurbidimetric determination of amylase, [Guth & others] 480
secretion, alterations in, as a psychosomatic disorder, [Smolen] 230
weight, [Ashworth & others] 143
with surgical cure of islet cell tumor, [Pickard & others] 488
PANCREATECOMY, human total, [Gourevitch] 479; [Honjo & Araki] 481
retroperitoneal leiomyosarcoma and, effects on metabolism, [Nardi] 64
PANCREATICOGASTROSTOMY, [Ingebrigtsen & Langfeldt] 151; [Ogilvie] 64
PANCREATITIS, acute, blood amylase in, [Foreign Letters] 306
acute, diagnosis, [Bockus & others] 392; [Foreign Letters] 306
acute, etiology, [Bockus & others] 392
acute, serum amylase in, [Foreign Letters] 306
acute, therapy, [Bockus & others] 392
acute colonic obstruction and, [Miln & Barclay] 63
obstructive, etiology, [Hendry] 58
pathogenesis, [Longo & others] 152
therapy, epidural block in, [Berk & Krumperman] 144
traumatic, temporary diabetes as a complication of, [Barnbrook] 50
PANHYPOPITUITARISM, diabetes and, Raben-Westermeyer growth hormone in, [Conn & others] 217
PATHOLOGY OF DIABETES, [Hamilton] *180
interpretation of diabetes, [Warren] *257
PATIENT PRESCRIBES FOR THE PHYSICIAN, [Fred Allen] *422
PANTOTHENIC ACID, deficiency, adrenal cortical function and, [Hurley & Morgan] 151
deficiency, carbohydrate metabolism and, [Hurley & Morgan] 151
PAPER CHROMATOGRAPHY, galactosemic urine investigations and, [Bickel & Hickmans] 144
PENICILLIN-LACTOSE, in burn therapy, lactosuria and, [Baar & Bull] 302
PERIODATE REACTION, blood sugar determination and, [Salo] 229
PHENOBARBITAL, neurogenic hypoglycemia and, [Queries and Minor Notes] 409
PHLORHIZIN, effects on cataract development in diabetic rats, [Patterson] 408
mobilization of glucose by, in patients with mental disorders, [Altschule & others] 469
PHOSPHATASE, alkaline, leukocyte glycogen and, [Valentine & others] 314
in liver, regeneration after lobectomy, effects of alloxan diabetes, insulin and Bayer 205 on, [Norberg] 154
PHOSPHATE, alkaline, in plasma, after hepatectomy, [Flock & others] 148
in plasma, in diabetic pregnancy, [Morgans] 63
in serum, effects of glucose and fructose on, [Smith & others] 312
metabolism, in kidneys, [Dratz & Handler] 395
PHOSPHOLIPIDS, excretion, factors influencing, [Kim & Ivy] 224
in coronary arteries, analysis of, in normal and diabetic arteries, [Lundbaek & Petersen] 309
in serum, absorption montmorillonite, [Nikkilä & Oker-Blom] 227
in serum, diabetic glomerulosclerosis and, [Engelberg & others] 220
metabolism, effects of pancreatectomy on, [Nardi] 64
PHOSPHORUS, in blood, hyperglycemia and, [Queries and Minor Notes] 311
radioactive, carbohydrate and phosphate metabolism studies in kidneys and, [Dratz & Handler] 395
PHOSPHORYLATION, enzymic, [Long] 225
liver phosphate turnover in alloxan diabetes and, [Sacks] 411
PHYSICIANS, diabetes in, [Mirsky & others] 226
PHYSIOLOGICAL CONGRESS, 1953, *431
PITUITARY EXTRACTS, bovine, relation of diabetogenic activity to growth hormone content, [Reid] 410
diabetogenic action of different preparations of growth hormone, [Houssay & Rodriguez] 482
effects of pituitary extracts and growth hormone preparations on islets and pancreas, [Haist & others] *112
effects of pituitary hormones on metabolism of isolated tissue [Krahl] *26
insulin-like action of growth hormone, [Ottaway] 487
PITUITARY, hypopituitarism with diabetes, [Poulsen] *7
PITUITARY GLAND, disease, insulin tolerance and, [Aziz & Bebawi] 144; [Soffer] 313
fasting ketosis in hypophysectomized rats, [Bahner & Taylor] 471
fatal hypoglycemia in a diabetic patient with pituitary necrosis, [Alexander] 469
Simmonds' and diabetes [Poulsen] *7
growth hormones of: See Growth hormone; Somatotropin
insufficiency, dwarfism and, [Steiner] 413
secretion, alterations in, as a psychosomatic disorder, [Smolen] 230
PLACENTA, glucose production in fetus and, [Villee] 315
PLASMA, diabetic, "anti-insulin" activity of, [Bornstein] 52
electrolytes, in diabetic acidosis, [Nichols & Nichols] 310
water, in diabetic acidosis, [Nichols & Nichols] 310
PLASMODIUM BERGHEI, infections, in rats, blood sugar level in, [Mercado] 406
POISONING, in infants and children, blood pyruvic acid in, [Passweg] 64
POLYARTERITIS NODOSA presenting as acute diabetes, [French] 478
POLYCYTHEMIA, retinal venous thrombosis and, [Birge] 144
POLYNEURITIS, diabetes and, BAL in, [Guthrie] 150
POLYSACCHARIDES, in serum, in diabetics with and without degenerative vascular disease, [Berkman & others] 391

POLYURIA, alloxan diabetes and, sugar excretion in, [Cohen] 52
POSTGRADUATE COURSE IN DIABETES, 1953—*166 and *341; 1954—*428 and *506
POSTPRANDIAL SYNDROME, stomach resection and, [Medical Literature Abstracts] 309
POTASSIUM, acidosis and, [Crampton & others] *1
diabetic coma and, [Fajans] 397
diabetic coma, treatment with, [Crampton & others] *1
in plasma, effects of intravenous glucose after pretreatment with insulin or epinephrine, [Dury] 219
hypopotassemia in diabetic coma, [Crampton & others] *1
intravenous infusion, liver glycogen and, [Seibert & others] 158
metabolism, diabetes and, [Aikawa & others] 215
relationship to "steroid diabetes" in general and steroid hormone-induced insulin resistance in particular, [Kinsell] 482
retention, growth hormone and, in adrenalectomized rats, [Stein & others] 231
serum, in diabetic coma, [McCullagh] *175
tolerance, glutathione and, in adrenalectomized mice, [Martorano & others] 405
POTASSIUM CHLORIDE, inhibition of diabetic enhancing effect of ACTH and, [Glafkides & others] 56
PREDIABETES, pregnancy and: See under Pregnancy
PREGNANCY, blood sugar level in, [Jackson] 59; [Queries and Minor Notes] 155
care of infant of diabetic mother, [Queries and Notes-Bolinske] 488
diabetes and, acidosis in, [Jones] 223; [Pedowitz & Shlevin] 155
diabetes and, Cesarean section: See Cesarian section
diabetes and, fetal mortality and, [Hurd] 307
diabetes and hypoglycemia and, [Pedowitz & Shlevin] 155
diabetes and, management, [Brown & Mark] 52; [Ellis] 220; [Given] 397; [Heck] 222; [Hurwitz & Higano] 58; [Parmelee] 154
diabetes and, management, hormonal, [Pedowitz & Shlevin] 155
diabetes and, newborn infant and, [Parmelee] 154
diabetes and, plasma inorganic phosphate levels in, [Morgans] 63
diabetes and, prognosis, [Kade & Dietel] 224; [editorial] 477
diabetes and, toxemia in, [Hurwitz & Higano] 58; [Jones] 223; [Pedowitz & Shlevin] 155
diabetes and, toxemia in, retinal changes in, [Landesman & others] 60; [Snyder] 68
diabetic retinopathy and, [Landesman & others] 60
intrauterine roentgenography in determining fetal age, [Adams & others] 469
obesity and, [Richardson] 66
prediabetes and, [Annotations] 49; [Futcher & Long] 222; [Jackson] 59
prediabetes and, prognosis, [Kade & Dietel] 224
PRESIDENT'S MESSAGE, [Sprague] *425
President's Report, [Allan] *330
PRISCOLINE, arteriosclerosis obliterans and, [Texter & others] 232
effects on ketonuria, liver glycogen and liver lipids, [Janes & Boeke] 151
PRIZE FOR STUDENT ESSAY ON DIABETES, [editorial] *73; *341 and *508
PROCAINE, intravenous, vasodilator effects in peripheral arterial disease, [Jessar & others] 223
PROGESTERONE, effects on growth of islands of Langerhans, [Kerr & others] 152
PRONESTYL, arteriosclerosis obliterans and, [Texter & others] 232
PROTAMINE, estimation of, in protamine zinc insulin, [Robinson & Fehr] 66
PROTAMINE ZINC INSULIN, [Editorial] 396
assay, [Robinson & Fehr] 66
dosage, in tubercular diabetic, effect of isonicotinic acid hydrazide on, [Spiegelman & Quicgley] 313
effects on β-cell granules of the islets of Langerhans, [Nerenberg] 407
tubercular diabetics and, [Reaud] 410
PROTEINS, diet and: See Diet, proteins
extracts, from fishlens, cataracts and, [Shropshire & others] 67
effect of amount and type in breakfasts, on blood sugar levels [Addison & others] 469
in plasma, congenital deficiency in Wilson's disease, [Scheinberg & Gitlin] 67
in plasma, effects of cortisone, ACTH and adrenalectomy on, [Schacter & Entenman] 158
in serum, absorption by montmorillonite, [Nikkilä & Oker-Blom] 227
in serum, allergic and blocking activity in, [Loveless & Cann] 225
in serum, diabetes and [Forker & Chaikoff] 149
in serum, electrophoretic study, [Rafsky & others] 228
metabolism, diabetes and, [Editorial] 395
metabolism, disturbance, diabetes and, [Schreier & Szybko] 412
metabolism, disturbance, tuberculosis in diabetic and, [Cooper & Boucot] 146
metabolism, influence of insulin on, [editorial, Lukens] *491
reversible association processes, [Steiner] 231
PROTHROMBIN TIME, thrombosis of central retinal vein and, [Cascio] 217
PRURITIS VULVAE, [Lynch] 61
PSORIASIS: See Skin, diseases
PSYCHOSOMATIC MEDICINE, evaluation, [Smolen] 230
PSYCHOTHERAPY, group, schizophrenia and, [Morrow & others] 154
PUBLIC HEALTH, interest in diabetes, [Ford] 477
PUPILS, effects of diabetic neuropathy on, [Pryor] 65
PYELONEPHRITIS, complications, [Review] 410
diabetes and, [Loomis] 405
PYRORACEMIC ACID: See Pyruvic acid
PYRUVATE, metabolism, effects of fluoroacetate on, [Busch & Potter] 145
metabolism, in mice, hereditary obesity-diabetes syndrome and, [Guggenheim & Mayer] 398
metabolism, influence of thioctic acid on, [Seaman] 312
PYRUVIC ACID, in blood, in children under various conditions, [Passweg] 64
in blood, response to intravenous glucose or insulin, [Amatuzio & others] 49

Q

QUININE SULFATE, nocturnal cramps with diabetes and, [Shuman] 229

R

RABEN-WESTERMEYER GROWTH HORMONE, effects on pituitary dwarf with diabetes, [Conn & others] 217
RADIOACTIVE INSULIN, [Elgee & others] *370
RAYNAUD'S SYNDROME, hydergine in, [Roberts & others] 228
REFRACTION, changes in, diabetes and, [Peterson] 228
RENAL DISORDERS: See Kidneys; Nephrosis
RESEARCH FELLOWSHIPS, American Diabetes Association, 509
RESPIRATORY QUOTIENT, effects of glucose on, in denervated and innervated muscle, [Gruber & others] 150
RETINA, arteriolar changes, in diabetic pregnancy with toxemia, [Snyder] 68
blood vessels of, diabetes and, [Friedenwald] 221; [Hartford] 399; [Heinsius] 223
blood vessels of, effects of blood oxygen, tension on, [Sieker & Hickam] 412
changes in, diabetes and, [Peterson] 228
RETINITIS, diabetic, [Heinsius] 223
diabetic, cysteine in, [Niedermeier] 407
diabetic, high-protein diet and, [Sparks] 230
diabetic, rutin in, [Niedermeier] 407
diabetic, therapy, [Niedermeier] 407; [Sparks] 230
hemorrhagic, cysteine in, [Niedermeier] 407
proliferans, diabetes and, [Minton] 63
RETINOPATHY, diabetes and, [editorial, Friedenwald] *237
diabetes and, [Givner] 222; [Marr] 62; [Murphy] 487; [Warren] *260
diabetes and, aneurysms in, [Friedenwald] 221
diabetes and, in infants and children, [Seigel] 230

diabetes and, intercapillary glomerulosclerosis and, [Agatston] 215
diabetes and, prognosis, [Cordes] 217
diabetes and, toxemia of pregnancy and, [Landesman & others] 60
diseases affecting renal glomeruli and, [Gartner] 306
effect on vision of diabetics, [Cordes] 473
recovery from, [editorial, Friedenwald] °72
recovery from, [Poulsen] °7
scleroderma and, [Gartner] 306
x-ray therapy, [Trueman & others] °13
RONIACOL, arteriosclerosis obliterans and, [Texter & others] 232
RUBEOSIS IRIDIS, diabetes and, prognosis, [Cordes] 217
secondary glaucoma and [Queries and Minor Notes] 488
RUTIN, diabetic retinitis and, [Niedermeier] 407

S

SACCHARIN, as noncaloric sweetener in canned fruit, [Anderson & others] 469
ST. LOUIS DREYPAK, [Olmsted & others] °37
SALICYLATE, effeects on cortisone-induced hyperglycemia and glycosuria, [Smith] 230
SALIVARY GLANDS, calculi: See Sialolithiasis
SCHIZOPHRENIA, hormonal imbalance in, [Nadeau & Rouleau] 487
insulin in, effects on serum citric acid, [Gottfried & others] 398
insulin shock therapy in, [Evseeff] 148; [Morrow & others] 154
insulin shock therapy in, effect on blood cholesterol level, [Goodman & Kanter] 56
insulin tolerance in, [Nadeau & Rouleau] 487
SCLERODERMA, retinopathy and, [Gartner] 306
SCURVY, effects of insulin on glucose metabolism in, [Stewart & others] 231
SECRETARY'S REPORT, [Reed] °331
SERUM, filtration rate through excised blood vessels, [Wilens & McCluskey] 233
SERUM SICKNESS: See Allergy
SEX, diabetes and, in partially pancreatectomized rats, [Rodriguez] 311
SIALOLITHIASIS, diabetes and, [Bartelheimer] 215
SIMMONDS' DISEASE, with recovery from diabetic retinopathy, [Poulsen] °7
SKF 688A: See Dibenzyline
SKIN, diseases, diabetes and, [Kern] 308
diseases, insulin hypoglycemia in, [Weitzner] 69, 70
temperature, in arteriosclerosis obliterans therapy, [Texter & others] 232
SLEEP PARALYSIS, insulin hypoglycemia in, [Weitzner] 69
SOCIAL ASPECTS OF DIABETES, [Grunberg & Blair] °277
SODIUM, retention, growth hormone and, in adrenalectomized rats, [Stein & others] 231
SODIUM CITRATE, vascular disease and, [Foreign Letters] 55
SODIUM DIETHYLDITHIOCARBAMATE, islands of Langerhans and, [Davis] 219
SODIUM GLUCONATE, effects on urine ketones, in diabetic rats, [Koster] 402
SODIUM LACTATE, hypertonic, intercapillary glomerulosclerosis and, [Neubauer & Sindoni] 310
renal insufficiency and, [Neubauer & Sindoni] 310
SOMATOTROPIN, effects in experimental animals, [Abaza & others] 390
effects on development of fetus, [Annotations] 49
SORBITOL, as sugar substitute, [Olmsted] °132
SPLEEN, oxygen consumption, effects of Eck fistula on, [Hallett & others] 57
SPLENECTOMY, effects on liver blood flow, [Hallett & others] 57
in hemochromatosis associated with portal hypertension, [Dunlap & others] 54
SPRUE, ACTH in, [Colcher & others] 393
cortisone in, [Colcher & others] 393
STARVATION, effects on β-cell granules of the islets of Langerhans, [Nerenberg] 407
hematopoiesis in, [Evans] 305
similarity of biochemical difficulties to diabetes, [Stetten] 313
STATISTICS ON DIABETES, report of Committee on Statistics [Marks, chairman] °325
STEROIDS, adrenocortical, carbohydrate metabolism and, [Cohn] 53; [de Bodo & others] 147, 394
diabetes and, [editorial, Sprague] °159
diabetes in man and, [Bookman & others] °100
diabetes, relationship of potassium to, [Kinsell] 482
formaldehydogenic, diabetes and, [Wolfe & Paschkis] 70
STOMACH, acidity, insulin and, [Levy & others] 60
surgery, hypoglycemia and, [Medical Literature Abstracts] 309
surgery, postprandial syndrome and, [Medical Literature Abstracts] 309
STRESS, blood glucose and, [Hinkle & Wolf] 307
blood glycolysis and, [Vaccari & Rossanda] 68
blood ketone bodies and, [Hinkle & Wolf] 307
Cushing's syndrome and, [Secco] 67
diabetes and, [Hinkle & Wolf] 307
diuresis and, [Hinkle & Wolf] 307
fructose metabolism and, [Drucker & others] 219
realimentation following fasting and, [Wilhelmj & others] 70
studies of the interdependent effects of stress and the adrenal cortex on carbohydrate metabolism in man, [Burns & others] 472
urinary 17-ketosteroids and, in alloxan diabetic rabbits, [Koref & Errazuriz] 308
SUCARYL CALCIUM, excretion, [Schoenberger & others] 411
metabolic effects of, [Schoenberger & others] 411
toxicity, [Schoenberger & others] 411
SUCARYL SODIUM, as noncaloric sweetner in canned fruit, [Anderson & others] 469
SUCCINIC ACID, labeled, conversion to glucose, [Abraham & Chaikoff] 390
SUGARS, action of insulin on transfer of, across cell barriers, [Goldstein & others] 478
action of muscular work on transfer of, across cell barriers, [Goldstein & others] 478
in cerebral venous blood, desoxycorticosterone glucoside and, [Schieve & Wilson] 157
in blood, rapid estimation with Galatest reagent, [Guest & Lestradet] °350
in spinal fluid, rapid estimation with Galatest reagent, [Guest & Lestradet] °350
invert, blood sugar and, in insulin-induced experimental hypoglycemia, [Bhattacharya & others] 51
invert, metabolism, comparison with glucose metabolism, [Bertino & others] 391, [Smith & others] 67
invert, rapid injections of, [Frost & others] 149
invert, tolerance as compared to dextrose, [Frost & others] 149
reducing, in urine, after administration of 3-methyl glucose, [Campbell & Young] 145
utilization and excretion of infused glucose, fructose and invert sugar, [Bertino & others] 471
SULFHYDRYL, in plasma, effects of cortisone, ACTH and adrenalectomy on, [Shacter & Entenman] 158
SURGERY, carbohydrate metabolism in postoperative period, [Hayes & Brandt] 150
diabetes, management of foot lesions in, [Miller] 63
hyperinsulinism and, [Hellstrom] 223
in diabetes, [Azar], 470; [Bernhard & Bizot] 471
liver physiology and, [Child & Payne] 145
SWEETENERS, NONCALORIC, in canned fruits. [Anderson & others] 469
SYNTHALIN A, degeneration of *a*-cells of pancreatic islets and, [Davis] 219

T

TEMPERATURE, effects on cortisone's effectiveness, [Scherr] 229
TESTES, interstitial cell tumor of, insulin resistant diabetes and, [Lopis & others] 61
TESTOSTERONE, diabetes development and, [Rodriguez] 312
effects on growth of islands of Langerhans, [Kerr & others] 152
growth hormone and, effects on muscle glycogen in hypophysectomized female rats, [Bowman] 392
impotence of diabetes and, [Schept] 229
propionate, effects on blood lipids, in diabetics with arteriosclerosis, [Dewind & others] 395
THIAMINE: See Thiamine hydrochloride
THIAMINE HYDROCHLORIDE, de-

ficiency, fat synthesis and carbohydrate metabolism in, [Gruber] 57
THIOCTIC ACID, in pyruvate and *a*-ketoglutarate oxidation, [Seaman] 312
THIRST, diagnostic significance, [Holmes & Montgomery] 399
mechanism, [Holmes & Montgomery] 399
THROMBOPHLEBITIS, hydergine in, [Roberts & others] 228
THROMBOSIS, retinal venous, etiology, [Birge] 144
retinal venous, metabolic aspects of, [Cascio] 217
THYROID, ACTH with, dwarfism associated with hypoglycemia and convulsions and, [Steiner] 413
disease, breast cancer and, [Repert] 311
disease, insulin tolerance and, [Aziz & Bebawi] 144
THYROXINE, effects on hereditary obesity-diabetes syndrome in mice, [Mayer & others] 406
TISSUE, electrolytes, effects of insulin and epinephrine on, in normal and demedullated rats, [Dury & Moss] 147
ketonic substance in, effect on ketone body excretion, [Stewart & Young] 231
TOXEMIA, of pregnancy: See Pregnancy
TREASURER'S REPORT, [Olmsted] *332
TREATMENT OF DIABETES, dietary instruction for the diabetic, [Behrman] *271
group therapy of obese diabetics, [Goodman & others] *280
management in children, [Chute] *268
selective technic according to severity, [Colwell] *262
TUBERCULOSIS, diabetes and, [Cooper & Boucot] 145
diabetes and, incidence, [Reaud] 409; [Speck & others] 68
diabetes and, isoniazid in, [Spiegelman & Quicgley] 313
diabetes and, mortality, [Foreign Letters] 149; [Reaud] 410
diabetes and, prognosis, [Ferrara] 306
diabetes and, therapy, [Reaud] 410
TUBULAR MECHANISM, glucose and, [Adams] 142
TUBULAR REABSORPTION, of glucose, effects of desoxycorticosterone glucoside on, [Despopoulos & Kaufman] 53
TYROSINE, regulation of food intake and, [Hill & others] 58

U

UNDERNUTRITION TREATMENT of diabetes mellitus, [Queries and Minor Notes—Jones] 489
URINARY TRACT, infections, diabetes and, [Barnard & others] 215
URINE, excretion, alloxan diabetes and, [Cohen] 52
URTICARIA: See Skin, diseases

V

VASCULAR DISEASE: See Blood vessels
VASOSPASTIC DISEASES: See Diseases, Vasopastic
VEINS: See Blood vessels
VITAMIN C, adrenal cortex and, [Hughes & others] 58
arthritic lesions and, in vitamin C deficient guinea pigs, [Hughes & others] 58
VITAMINS, deficiency, diabetes and, [Beidleman] 303
diabetic neuropathy and, [Fortuin & Wassing] 56
VOMITING, acidotic, in infants and children, blood pyruvic acid in, [Passweg] 64
VON GIERKE'S DISEASE: See Glycogen, storage disease

W

WATER, in body, disease and, [Moore & others] 63
in body, relationship to amount of fat in body, [Hardy & Drabkin] 57
in plasma, effects of intravenous glucose after pretreatment with insulin or epinephrine, [Dury] 219
in plasma and erythrocytes, diabetic acidosis and, [Nichols & Nichols] 310
retention in diabetic acidosis, [Darrow & Pratt] 218
WILDER, Russell M., retirement, [editorial] *417
WILLIS, Thomas, biographical note, [Allan] *74
WILSON'S DISEASE, ceruloplasmin in serum in, [Scheinberg & Gitlin] 67

Y

YOUNG'S SYNDROME, [Abaza & others] 390

Z

ZINC, in blood, determination, [Maske & Wolff] 405
ZINC^{65}, radioactive, effects on pancreas after prolonged administration, [Sherrill & Wick] 312
ZINC INSULIN, two new types of long-acting insulins [Novo], [Izzo & others] *358
various preparations, [Hallas-Moller & others] 398

Errata

p. 53 Cohen, E. M. In thirteenth line delete the first *to*.

p. 53 Creeth, J. M. In sixth line change *its* to *it*.

p. 55 Foreign Letters (Paris). In twelfth line *influence* should read *influenced*.

p. 58 Hart, James C. Second line should read: pend upon early detection and adherence to the recommendations.

p. 63 Miller, James W. In third line change *in* to *is*.

p. 64 Nadbath, Rudolph P. and Fauteux, Louis Z. In first line delete comma after *Lipemia retinalis*.

p. 151 Ingebrigtsen, R. and Langfeldt, E. Title should read: Pancreaticogastrostomy.

p. 154 Parmelee, A. H. Last sentence should read: Whether administration of glucose and the use of epinephrine to prevent hypoglycemia or to treat it if present is indicated or not is an unsettled question.

p. 156 Rippy, Edwin L. In thirteenth line *thought* should read *though*.

p. 221 Friedenwald, Jonas S. In seventh line *After* should read *Often*. In seventh, eleventh, and fourteenth lines *aneurysons* should read *aneurysms*.

p. 226 MacQueen, A. T. In third line add the word *level* after *diabetogenic*.

p. 231 Stewart, H. B. and Young, F. G. In eighth line *rates* should read *rats*.

p. 302 Allen, O. P. In seventh line delete *during*. In thirteenth line *syptoms* should read *symptoms*.

p. 308 Kern, Arthur R. Change author's middle initial to *B*.

p. 312 Sherrill, James W. and Wick, Arne J. Change Wick's middle initial to *N*.

p. 312 Ronchese, Francesco and Kern, Arthur B. In journal title *Sypth.* should read *Syph.*

p. 391 Bell, David M.; Burns, Thomas; and Schieve, James. In fourth line *wee* should read *were*.

p. 393 Cook, Margaret and Lorber, Victor. In fifth line *an* should read *as*.

p. 408 Patz, Arnall. In last line add *of* after *some*.

p. 413 Steiner, Matthew M. Add to end of article: anterior pituitary, perhaps secondary to a congenital defect of the hypothalamus, with fractional deficiencies of hormones concerned with growth, the thyroid, gonads, and adrenal cortex; and that the hypoglycemia is the result of hypofunction of one or more of these "target" organs.

AUTHOR INDEX

In this Index are the names of the authors of articles which have appeared in DIABETES and those whose articles have been abstracted in the Journal during 1953. The asterisk (*) preceding the page reference indicates that the article appeared in full in DIABETES.

For subject index see page 512.

A

Aarseth, S., 302
Abaza, A., 390
Abbott, W. E., 219
Abraham, S., 142, 390
Acevedo, D., 469
Ackerman, J. L., 392
Adams, A. V., 142
Adams, T. W., 469
Addison, V. E., 469
Adlersberg, D., *100, 393
Agatston, H. J., 215
D'Agostino, A. W., 223
Agress, H., *37
Aguirre, N., 404
Aikawa, J. K., 215
Alagille, D., 144
Albertsson, V., *184
Albrink, M. J., 306
Alexander, G. H., 49
Alexander, R. I., 469
Allan, F. N., *74, *330, *337
Allen, F. M., 215
Allen, Fred., *422
Allen, O. P., 302
Altschule, M. D., 142, 469
Alvarez, W. C., 49
Amatuzio, D. S., 49, 390
Ammentorp, P., 62, 479
Anderson, E. E., 419
Anderson, G. E., 470
Anderson, L. L., 228
Annotations, 49, 142, 143
Araki, C., 481
Archdeacon, J. W., 58
Arteta, J. L., 50
Ashby, D. W., 470
Ashworth, M. A., 143
Audy, G., 143
Azar, G., 470
Azerad, E., 144
Aziz, S., 144

B

Baar, S., 302
Bacchus, H., 470
Bach, I., 302
Bacon, J. S. D., 303
Bahner, F. W. R., 471
Baird, V. C., *299
Baker-Bates, E. T., 156
Barclay, T. H. C., 63
Barford, B., 390
Barnard, D. M., 215
Barnbrook, D. H., 50
Barson, L. J., 490
Bartelheimer, H., 215, 471
Bates, M. W., 226, 405
Batts, A. A., 230
Beal, J. M., 67
Beardwood, Jr., J. T., *13, 303, *334
Bearn, A. G., 303
Beary, D. F., 482
Beaser, S. B., 50
Beattie, J., 390
Beatty, C. H., 391
Beaudoin, R., 216, 490
Beautyman, W., 226
Bebawi, E., 144
Beecher, H. K., 216
Behrman, Deaconess M., *271
Beidleman, B., 303
Bell, D. M., 50, 391
Bell, E. T., *125, *376
Bennett, L. L., 56, 230, 413
Berg, J. W., *365
Berger, S., 149, 221
Bering, E. A., Jr., 63
Berk, E. J., 144
Berkman, J., 391
Berkman, S., 481
Berner, J. H., Jr., 216
Bernhard, C. M., 471
Bernard, H., 471
Bernstein, L. M., 51
Bertino, J., 391, 471
Best, C. H., *321, *338
Bhattacharya, B. K., 51
Bickel, H., 144
Bicknell, E. A., 303
Billing, B. H., 303
Birdsong, M., 471
Birge, H. L., 144
Bishop, C. T., 471
Bizot, W. H., 471
Blair, J. L., *277
Bleehen, N. M., 216
Bleisch, V. R., 51
Block, M. A., 148, 397
Blotner, H., *47
Blum, H. P., 479
Bockus, H. L., 392
Boeke, L. S., 151
Bogoch, A., 392
Bohan, E. M., 392
Boldt, M. H., 392
Boldt, S. K., 392
Boling, L., 402
Bolinske, R. E., 488
Bollman, J. L., 51, 148, 397
Bondy, P. K., 392
Book review, 145
Bookman, J. J., *100
Bornstein, J., *23, 52, 472
Bortz, D. W., 304
Bortz, E. L., *235, *334
Bothwell, T. H., 61
Bottger, H., 216
Boucot, K., 145
Boulin, R., 472
Bounds, G. W., Jr., 151
Bowman, R. H., 392
Brandaleone, H., *458
Brandman, O., *194
Brandt, R. L., 150
Bray, P. T., 52
Brewster, W. R., Jr., 216
Brill, A. A., 228
Broacha, S. B., 51
Brofman, B., 146
Brooks, L., 63
Brousseau, E. R., 392
Brown, A. W., 52
Brown, D. H., 392, 407
Brown, D. M., 409
Brown, E. M., Jr., 52
Brown, M., 53
Brown, R., 484
Browne-Mayers, A. N., 477
Bruch, E., 217
Bryans, F. E., *100
Bull, J. P., 302
Bunker, J. P., 216
Burns, T. W., 50, 391, 396, 472
Busch, H., 145

C

Calhoun, W. W., 153
Campbell, A. M., 62
Campbell, P. N., 145
Cann, J. R., 225
Cant, D., 304
Carbonaro, L., 307
Carbonnell Aguilar, C. D., 304
Carr, J., 401
Carreras, M. A., 145
Carter, F. R., 233
Cascio, G., 217
Caso, E. K., *275, 472
Cathey, W. J., 314
Cavallero, C., 473
Chaikoff, I. L., 142, 145, 149, 152, 158, 390, 399, 405, 413
Chambers R. D., 390
Chao, D. H. C., 62
Cheng, T. O., 473
Chiménes, H., 472
Child, C. G., III, 145
Chinn, H. I., 153
Chitwood, W. R., 304
Chute, A. L., *187, *268
Claycomb, C. K., 314
Cohen, C., 484
Cohen, E. M., 52

Cohn, C., 53, 304
Colcher, H., 393
Coleman, M. C., 393
Colwell, A. R., *262
Conn, J. W., 217
Constantinides, P., 473
Cook, M., 393
Cooper, D. A., 145
Cordes, F. C., 217, 473
Corey, H., 228
Cori, C. F., 393
Cori, G. T., 393, 399, 400, 403
Cornblath, M., 392, 407
Cornforth J. W., 217
Correspondence, 393, 394
Cox, H., 484
Craig, J. W., 146, 219
Crampton, J. H., *1
Creery, R. D. G., 394
Creeth, J. M., 53, 218
Crosnier, J., 153
Crossen, G. E., 231
Cruz-Horn, A., 471
Cummins, A. J., 146

D

Daeschner, C. W., 146
Dalle Coste, P., 402
Danowski, T. S., 53, 474
Darrow, D. C., 218
Daughaday, W. H., 392, 407
Daum, K., 393, 469
Davidson, S., 218
Davis, J. C., 219
Dawson, N., 391, 471
De—For proper names beginning with prefix "de," see under name following prefix with exception of English and American names.
de Bodo, R. C., 146, 394
De Duve, C., 474
del Greco, F., *467
Dejean, F. A., 475
Dell Cort, A. P., 60
Delore, P., 147
De Moor, P., 52
Denison, M. E., 234
Derus, G. J., 487
Desneux, J. J., 65
Despopoulos, A., 53
Deuil, R., 153
Dewind, L. T., 394
DeWitt, S., Jr., 404
Diaz, C. J., 304
Dickens, J., 310
Dickie, M. M., 51, 405
Dietel, H., 223
Di Gilio, M. M., 59
Dine, M. S., *206, 305
Doerschuk, A. P., 147
Dohan, F. C., 52
Dolger, H., 395, 475, 489
Dorfman, R. I., 222
Douglas, R. G., 60
Dowd, G. C., 53
Downie, E., 53
Doyle, B., 229
Drabkin, D. L., 57
Drachman, S. R., *100, 393
Dratz, A. F., 395
Drazin, Morris L., *443
Drey, N. W., *37
Dross, R. L., 68
Drucker, W. R., 146, 219
Drury, D. R., 147, *475
Duncan, G. G., 219, *353, 475
Dunlap, R. W., Jr., 54
Dury, A., 147, 219, 395

E

Eberlein, W. R., 476
Edelman, I. S., 63
Editorials, 54, 219, 220, 305, 395, 396, 476, 477
Editorials and Comments, 220, 305
Elgee, N. J., *370
Ellis, A., 220
Elrick, H., 396
Elvehjem, C. A., 220
Endrys, J., 402
Engel, F. L. 396, 472
Engel, G. L., *93
Engelberg, H., 148, 220, 221
Engelhardt, H. T., *299
Enhörning, G., 407
Entenman, C., 158
Erhard, L., 53
Errazuriz, H. O., 308
Escovitz, W. E., 148
Eskind, I. B., 477
Esselen, W. B., 469
Essellier, A. F., 396
Ettinger, R. H., 312
Evans, C., 396
Evans, J. D., 305
Evans, M. A., *112
Evarts, E. V., 477
Everett, W. G., 221
Evseeff, G. S., 148

F

Fabrykant, M., 397
Fajans, S. S., 217, 397
Faloon, W. W., 477
Farrant, J. L., 55
Farrell, H. W., *85
Fauteux, L. Z., 64
Fehr, K. L. A., 66
Feinblatt, T. M., 55
Feinmann, E. L., 481
Feldman, M., 148
Fellers, C. R., 469
Felts, J. H., Jr., 215
Ferguson, E. A., Jr., 55
Ferguson, S., 232
Ferrara, M. A., 306
Ferraris, A., 152
Fisher, R. B., 216
Flock, E. V., 148, 397
Foa, P. P., 149, 221
Foley, E. F., 51
Follette, J. H., 306, 314
Ford, M. J., 477
Foreign Letters, 55, 149, 306, 378
Forker, L. L., 149
Fortuin, F., 55
Francisco, R., 56
Frankel, L., *280
Franklin, W., 477
Freedman, L. R., 52
Freidell, H. V., 226
French, G., 478
French, R., 471
Friedberg, F., 490
Friedenwald, J. S., *72, 221, *237
Friedman, G. J., *458
Frost, D. V., 149
Frost, P., 67
Futcher, P. H., *31, 222
Futterman, P., 226

G

Gabiga, A. M., *358
Galley, A. H., 397
Garland, H., 478
Gartner, S., 306
Geiger, E., 150
Gentry, Jr., H. E., *285
George, R., 56
Gibson, J. M., 222
Gibson, M., 66
Gifford, J. P., 489
Gill, R. J., *353
Ginsberg, J. R., 67
Gitlin, D., 67
Given, W. P., 397
Givner, I., 222
Glafkides, C. M., 56
Godlowski, Z. Z., 56
Goetz, F. C., 62
Gofman, J. W., 56, 220, 401
Goldstein, M. S., 478
Goodman, J. I., 158, *280, 479
Goodman, J. R., 56
Gottfried, S. P., 397
Gourevitch, A., 479
Grande, F., 304
Graubarth, H., 62, 479
Green, A. A., 308
Green, H. D., 66
Greenberg, R. M., 486
Greene, J. A., *299
Greenhouse, B., 57
Greer, R., 391
Grindlay, J. H., 51, 397
Grinspoon, L., 479
Gruber, C. M., Jr., 150
Gruber, M., 57
Grunberg, A., *277
Grunebaum, H. U., 469
Guest, G. M., 62, *350, *415, 479, 485
Guggenheim, K., 398
Gupta, N. N., 480
Guth, P., 480
Guthrie, T. C., 150
Gutmann, M. J., 398
Gyulai, E., 302

H

Haft, D. E., 226
Haist, R. E., *112, 143, 152, *295
Hald, P. M., 403
Haley, H. B., 63
Hall, G. F. M., 150
Hallas-Moller, K., 398
Hallenback, G. A., 54
Hallett, E. B., 57
Hamilton, J. D., *180
Hand, A. M., *85
Handler, P., 395
Hanlon, D. G., 54
Hardy, J. D., 57
Harrell, G. T., Jr., 215
Harris, L. V. D., 306
Hart, J. C., 58
Hartford, J. J., 398
Harvey, H. I., 480
Harwood, R., *43
Hassid, W. Z., 142
Hatch, F. T., 150

Haugaard, E. S., 399
Haunz, E. A., 222
Hayes, M. A., 150
Haynes, R., 222
Heck, W., 222
Heffner, G. P., 399
Heiffer, M. H., 470
Heinson, A. J., 403
Heinsius, E., 223
Hellstrom, J., 223
Helmer, O. M., *345
Hendry, W. G., 58
Henry, R. J., 481
Henry, W. L., 478
Henson, W. C., 399
Hickam, J. B., 412
Hickmans, E. M., 144
Higano, N., 58
Hill, R. G., 58
Hinkle, L. E., Jr., 307
Hirsch, E. F., 307
Hirson, C., 399, 481
Hoet, J. P., *322
Hoffman, W. S., 51
Hoffmaster, J., *358
Hogness, J. R., *370
Hollander, L., 481
Hollingsworth, D. R., 472
Hollis, B. H., 481
Holmes, J. H., 399
Holton, G. W., 57
Honjo, I., 481
Horwitz, O., 223
Hotta, S., 399
Houssay, B. A., 482
Hubata, R., 224
Huddlestun, B., 53, 478
Huff, S., 53
Huggins, R. A., 158
Hughes, J. S., 58
Hughes, R. F., 58
Humoller, F., 234
Humphrey, L. M., *122
Hurd, J. B., 307
Hurley, L. S., 151
Hurst, A. T., 481
Hurwitz, D., 58
Hutchens, T. T., 314
Hymes, J., *199
Hynes, T. V., 392

I

Iannaccone, A., 223
Illingworth, B., 399, 400, 403
Ingebrigtsen, R., 151
Ingle, D. J., *122, 307, 400, 482
Isaac, G. H., 414
Isaac, R. J., 52
Ison, E. C., 58
Ivy, A. C., 224
Izzo, J. L., *358

J

Jackson, R. L., *90, *206, 305, 308, *365
Jackson, S. H., 151
Jackson, W. P. U., 58
Jacobi, M., 67
Jaharaus, R. C., 473
Janes, R. G., 151
Jeanneret, R. L., 396
Jefferies, W. McK., 219
Jeghers, H., 157
Jersild, M., 398
Jessar, R. A., 223
John, H. J., 59, 152
Johnson, R. B., 234
Joiner, C. L., 59
Jones, H. B., 220, 401
Jones, W. S., 223
Jones, W. W., 58, 489
Joyner, C. R., Jr., 400

K

Kade, H., 223
Kaechele, E., 400
Kaiser, E., 224
Kanter, S., 56
Kaplan, R., *472
Kark, R. M., 411
Karvinen, E., 401
Karvinen, M. J., 401
Kaswin, A., 471
Katz, B., 53
Kaufman, E. H., 53
Keerberghen, J. Van, 401
Keiding, N. R., 152
Kelter, J. J., 408, 488
Kempe, C. H., 401
Kenny, A. J., *187
Kerbel, N. C., 143
Kerly, M., 143
Kern, A. B., 308, 312
Kerr, E. H., 152
Khedroo, L. G., 59
Kiang, S. P., 146, 394
Kibler, R. F., 401
Kim, K. S., 224
Kimmelsteil, P., 402
Kinash, B., *112
Kinsell, L. W., 391, 394, 402, 471, 482
Kirtley, W. R., *345
Kjems, E., 225
Klinger, R., 402
Klotzbucher, E., 59
Knick, B., 402
Knight, W. A. Jr., 483
Koch, S. L., 59
Kodousek, R., 402
Kolinsky, M., 53, 304
Komarov, S. A., 480
Koref, O., 308
Kornbleuth, W., 483
Koster, R., 402
Koszewski, B. J., 396
Krahl, M. E., *26, 224, 407
Krall, L. P., 485
Krumperman, L. W., 144
Kurtz, M., 146, 394
Kvale, W. F., 313
Kydd, D. M., 403

L

Lacey, A. H., 60
Lagario, F. A., 490
Landesman, R., 60
Landmann, W. A., 224
Lane, N., 394
Langfeldt, E., 151
Larner, J., 399, 403
Larsen, R., 469
Lashichenko, Z., 150
Lasser, R. P., 484
Laucks, S. P., 154
Laurence, D. R., 60
Lawrence, J. S., 306, 314
Lawrence, R. D., 60, 225, 403
Lazarus, S. S., 224, 315, 414
Lederer J., 401
Leduc, E. H., 484
Lee, J. M., 404
Lee, K. S., 150
Lee, N. D., *370
Lees, B., 304
Leevy, C. M., 225
Leinfelder, P. J., 151
Leon, A. P., 404
Leonard, S. L., 483
Lestradet, H., 144, *350, 404, 483
Levey, S., 219
Levine, R., 53, 478
Levy, B., 308
Levy, E. M., 60
Lewis, L. A., 308, 404
Li, C. H., 230
de Lima, T., 51
Lipsett, M. N., 404
Ljung, O., 61
Lober, P. H., 484
Lockwood, B. C., 309
Loewe, L., 484
Logan, V. P., 60
Lomax, D. H., 66
Long, C., 225
Long, D. A., 217
Long, N. W., Jr., 222
Longo, O. F., 152
Longwell, B. B., 413
Loomis, G. W., 405
Lopis, S., 61
Lorber, V., 393
Lorenz, T. H., 487
Louis, L. H., 217
Lourau, M., 484
Loveless, M. H., 225
Lowder, R. J., Jr., 49
Lowell, F. C., 477
Loxley, R., 303
Lueck, A. G., 61
Lueth, H. C., 226
Luikart, W. M., 484
Luisi, A., 61
Lukens, F. D. W., 52, *160, *161, 000
Lumb, G., 226
Lundbaek, K., 309
Lyman, C. P., 484
Lynch, F. W., 61
Lyon, I., 152, 405

M

McArthur, J. W., 62
McCance, R. A., 486
McCluskey, R. T., 233
McCullagh, E. P., *160, *171
MacDougall, I., *112, 152
MacGrath, Jr., W. B., *453
McGuire, T. F., 70
McKnight, W. K., 154
MacLachlan, E. A., 62
Mach, R. S., 485
MacQueen, A. T., 226
Machella, T. E., 405
Mackenzie Shattock, F., 62
Mackler, B., 62, 479, 485
Maddock, R. K., 485
Madonick, M. J., 226
Majer, R. G., 485
Malandra, B., 473
Man, E. B., 306
Mandel, P., 407
Mann, D. E., Jr., 234

Mann, F. C., 148, 397
Marble, A., *73, 152, *335, 479
Margen, S., 391, 402, 471
Margolin, M., *285
Margolis, J., 226
Mark, M. S., 52
Marks, H. H., *71, *138, *325
Marks, P. L., 485
Marr, W. G., 62
Martin, M. S., 153
Marshall, L. W., 490
Martorano, J. J., 405
Maske, H., 405
Masri, M. S., 152, 405
May, C. D., 231
Mayer, J., 51, 216, 226, 309, 398, 405, 406, 486, 490
Medical Literature Abstracts 309
Meeks, R. C., *122, 307
Mellinger, G. W., *1
Mendell, H., 68
Mercado, T. I., 406
Mercer, E. H., 55
Michaels, G. D., 394, 402
Micklem, L. P., 62
Migone, A., 469
Milch, L. J., 153
Miller, J. P., 149
Miller, J. W., 63
Miller, M., 146, 219
Miln, D. C., 63
Milton, J. S. 489
Minton, J., 63
Mirand, E. A., 406
Mirsky, I. A., 226
Mithoefer, J., 62
Montgomery, A. V., 399
Montgomery, H., 223
Moore, F. D., 63
Moore, F. J., 404
Moreau, R., 153
Moreira, O., 486
Morgan, A. F., 151
Morgans, M. E., 63
Morrill, M. F., 62
Morrison, L. M., 227
Morrow, T. F., 154
Moss, L. D., 147
Moyer, J. H., Jr., 70
Muether, R. O., 483
Mukherjee, S. K., 486
Mullick, V., 478
Murphy, E. S., 487
Musser, M. J., 487
Myers, J. D., 401

N

Nadbath, R. P., 64
Nadeau, G., 487
Najjar, V. A., 227
Nardi, G. L., 64
Natelson, S., 397
Neher, G. M., 234
Nerenberg, S. T., *130, 407
Nesbitt, S., 49, 390
Neubauer, R. A., 310
Newcomb, A. L., *85
Newman, E., Jr., 64
Newman, H. W., 64
Nichols, G., Jr., 310
Nichols, J., 66
Nichols, N., 310
Niedermeier, S., 407
Nikkilä, E., 227
Nora, E., 490
Norberg, B., 154
Nordman, J., 407
Norton, H. I., 314

O

Oakley, W., 403
de Ocampo, G., 227
O'Connell, W., 225
Odeblad, E., 407
Odom, E. T., 407
Ogilvie, H., 64
Oker-Blom, N., 227
Olmsted, W. H., *37, *132, *332
Ortmeyer, D. W., *365
Oppenheimer, H. E., 487
Osborn, C. M., 406
Osnes, M., 407
Ottaway, J. H., 487
Ott, D. L., *365
Owens, J. E., 146
Owens, M. G., 142
De Oya, J. C., 304

P

Packer, R. M., Jr., 303
Page, I. H., 308, 404
Page, O. C., 227
Palmer, L. J., *1
Papaspyros, N. S., 66
Park, C. R., 392, 407
Parkhurst, B. H., 14_2, 469
Parkinson, T. J., 394
Parmelee, A. H., 154
Parrot, M. H., 469
Parry, T. M., 228
Partridge, J. W., 402
Paschkis, K. E., 70
Passweg, E., 64
Paterson, H., 56
Paterson, J. C. S., 57
Patterson, J. W., 408, 488
Patz, A., 408
Paugh, J. T., 412
Paul, J. T., 227
Payne, M. A., 145
Peck, F. B., *345
Pedowitz, P., 154
Peters, J. P., 306, 403
Petersen, E. S., *288
Petersen, K., 398
Petersen, V. P., 309
Peterson, J. H., 228
Petrides, P., 400
Phibbs, B. P., 307
Picard, H. N., *472
Picard, J. -L., 408
Pickard, K., 408, 488
Pihl, A., 64, 65
Pincus, I. J., 65
Pincus, J. B., 397
Pirart, J., 65
Please, N. W., 155
Pocock, D. S., 310
Polglase, W. J., 408, 409
Pollack, H., *177, *420, *497
Potter, V. R., 145
Poulsen, J. E., *7
Pratt, E. L., 218
Price, M., 53
Priestley, J. T., 313
Prior, K. M., 486
Pritchard, W. H., 146
Pryor, W. D., 65
Purmalis, A., 482

Q

Queries and Minor Notes, 66, 155, 228, 310, 311, 409, 488, 489
Quicgley, T. J., 313

R

Rafsky, H. A., 228
Ramfjord, S., 228
Rausch-Strooman, J. G., 489
Reaud, A., 409
Redisch, W., *194, 232
Redmond, R. F., 152
Reed, J. A., *165, *251, 311, *331, *333, *426
Reid, E., 410
Reinecke, R. M., 228
Repert, R. W., 311
Revell, S. T. R., Jr., 155
Revitch, E., 489
Reviews, 66, 410
Richards, R. K., 149
Richardson, A. W., 66
Richardson, G. O., *464
Richardson, J. S., 66
Richmond, G., 484
Ricketts, H. T., *72, 156, *288, 227, *316, 490
Rifkin, H., 391
Rippy, E. L., 156
Rix, D. M., 411
Robbins, S. L., 156, 157
Roberts, H. K., *37
Roberts, J. E., 228
Robertson, A., 314
Robillard, R., 410
Robinson, C. G., 311
Robinson, F. A., 66
Robinson, P. L., 156
Rodríguez, R. R., 311, 482
Rogers, J., 156, 157
Rombauts, M., 390
Romer, K., 216
Ronchese, F., 312
Root, H. F., 152, 157, 215, 413
Rose, William R., *472
Rosenbaum, L., 477
Rosenberg, B., 234
Ross, G., 391
Ross, P. H., 66
Rossanda, M., 68
Roth, J. L. A., 392
Rothenberg, R. E., 408, 488
Rouleau, Y., 487
Rubenstein, E., 226
Rugh, R., 308
Russell, N. G., Jr., 411
Russell, R. E., 405

S

Sacks, I., 411
Sacks, J., 411
Sagild, U., 479
Saka, M. O., 312
Sakamoto, A., 411
Salmon, R. J., 231
Salo, T. P., 229
Santamaria, L., 149, 221
Sauer, H., 489
Sauve, G., *31
Savard, K., 222
Savidge, R. S., 151
Saxton, R., 158

Scapellato, L., *467
Schaefer, L. E., *100
Scheinberg, H., 67
Schept, S. S., 229
Scherr, G. H., 229
Schieve, J. F., 157, 391
Schilling, J. A., 57
Schlichtkrull, J., 398
Schneeberg, N. G., *372
Schoenberger, J. A., 411
Schreier, K., 411
Schuster, D. B., *93
Schwartz, E. D., 158, *280
Schwenk, E., 233
Scott, J. L., Jr., 472
Seaman, G. R., 312
Searle, G. L., 158
Sebrell, W. H., Jr., 412
Secco, C., 67
Seeman, A., 471
Seibert, R. A., 158
Seitz, R., 216
Seligson, D., 312
Seltzer, H. S., 217
Setlow, R., 229
Shacter, B., 158
Shay, H., 480
Sheckman, E., 232
Sherlock, S., 303
Sherrill, J. W., 312, *475
Shlevin, E. L., 154
Shrifter, N., 49
Shropshire, R. F., 67
Shuman, C. R., 229
Siegel, E. P., 469
Siegel, R., 229
Sieker, H. O., 412
Silberstein, J. S., 412
Silides, D. N., 309
Silver, H. K., 401
Simmons, W. D., 480
Simpson, N. R. W., 490
Sindoni, A., 310
Siniscalco, M., 223
Sinkoff, M. W., 146, 394
Slater, E. C., 230
Smith, E. L., 408, 409
Smith, J. A., 149, 221
Smith, J. J., *13
Smith, J. L., 67
Smith, L. H., Jr., 312
Smith, M. J. H., 230
Smolen, E. M., 230
Smyth, F. S., 401
Snedecor, J. G., *453
Snowden, V. L., 69
Snyder, S. S., 60, 68
Soffer, L. J., 313
Sosa Gallardo, C. A., 152
Sparks, M. I., 230
Speck, C. D., Jr., 68
Spiegelman, A. R., 313
Sprague, R. G., *159, 313, *425
Spring, M., *199
Stacey, R. S., 60
Stadie, W. C., 399
Stears, J. C., 152
Steele, J. M., 232
Stein, J. D., Jr., 230
Stein, L., 151
Steiner, M. M., 412
Steiner, P. E., *288
Steiner, R. F., 231
Stephens, J. W., 413
Sterling, R. E., 413
Stern, K. G., 228
Stetten, D., Jr., 313
Stevenson, S. S., 53
Stewart, C. T., 231
Stewart, H. B., 231
Stirland, G. B., 231
Story, R. D., 215
Stradling, P., 396
Striker, C., *242, 413
Stutzman, F. L., 49, 390
Sveinsson, S. L., 62
Sweeney, J. S., 68
Swenson, M. J., 58
Swerdlow, J., 61
Szybko, V., 411

T

Tarrant, H. A., 392
Taverner, D., 478
Taylor, J. D., 411
Taylor, N. R. W., 471
Taylor, W. J., 401
Texter, C. E., Jr., 232
Thin, C., 314
Thomas, C., 404
Thorsen, R. K., 407
Thosteson, G. C., 232, 314
Tittle, C. R., 303
Tomkins, G. M., 145, 413
Tonks, D. B., 232
Tourneur, R., 472
Traut, E. F., 473
Treiber, H. T., 314
Tribby, C. L., 232
Trowbridge, G. F., 490
Trueman, R. H., *13
Tupikova, N., *288
Tuttle, W. W., 393
Tuttle, W. W., 393, 469
Tweedy, P. S., 470
Twiss, R. J., 233
Tyler, F. H., 408

U

Underbjerg, G. K. L., 58

V

Vaccari, F., 68
Valentine, W. N., 306, 314
Van Bruggen, J. T., 314
Van Eck, W. F., 306
Van Itallie, T. B., 226, 490
Van Keerberghen, J.: See Keerberghen, J. Van
Vanderbilt, M. J., 390
Varley, H., 151
Varroud-Vial, J., 390
Vere, D. W., 314
Viau, 472
Villee, C. A., 315
Viranyi, A., 302
Volk, B. W., 224, 315, 414
Vollmer, E. P., 405

W

Wachstein, M., 68
Wade, H. J., 481
Walaas, E., 414
Walaas, O., 414
Waldmann, E. B., 70
Walker, R. P., 311
Walsh, J. R., 234
Warren, S., *257
Wassing, H., 55
Watkins, A. G., 52
Waugh, J. M., 68
Webb, J. F., 414
Wehr, J., 402
Weinberg, T., 148
Weinstein, H. R., 149, 221
Weitzner, H. A., 69, 70
Werk, E., 472
Wertheimer, E., 483
Werthessen, N. T., 233
West, E. S., 314
West, K. M., 157
White, T. J., 225
Whitely, J. M., 469
Whitfield, A. G. W., 479
Wick, A. N., 147, 312, *475
Widdowson, E. M., 486
Wilens, S. L., 233
Wilhelmj, C. M., 70
Wilkey, J. L., 490
Williams, M. A., 490
Williams, R. H., *370
Wilson, R. H. L., 64
Wilson, W. P., 157
Wirth, P., 53
Wolf, S., 307
Wolfe, S. M., 70
Wolff, H., 405
Wollenman, O. J., Jr., 156
Womack, C. R., 70
Wong, T., *370
Wood, J. B., 471
Wood, M. D., 62
Woodward, H., Jr., 146, 219
Wrinch, D., 233

Y

Yardeni-Yaron, E., 483
Young, F. G., 145, 231
Yu, P. N. G., 233

Z

Zarrow, M. X., 234
Zimmerman, H. E., 234
Zinn, L. D., 481
Zwemer, R. L., 405
Zygmuntowicz, A., 62

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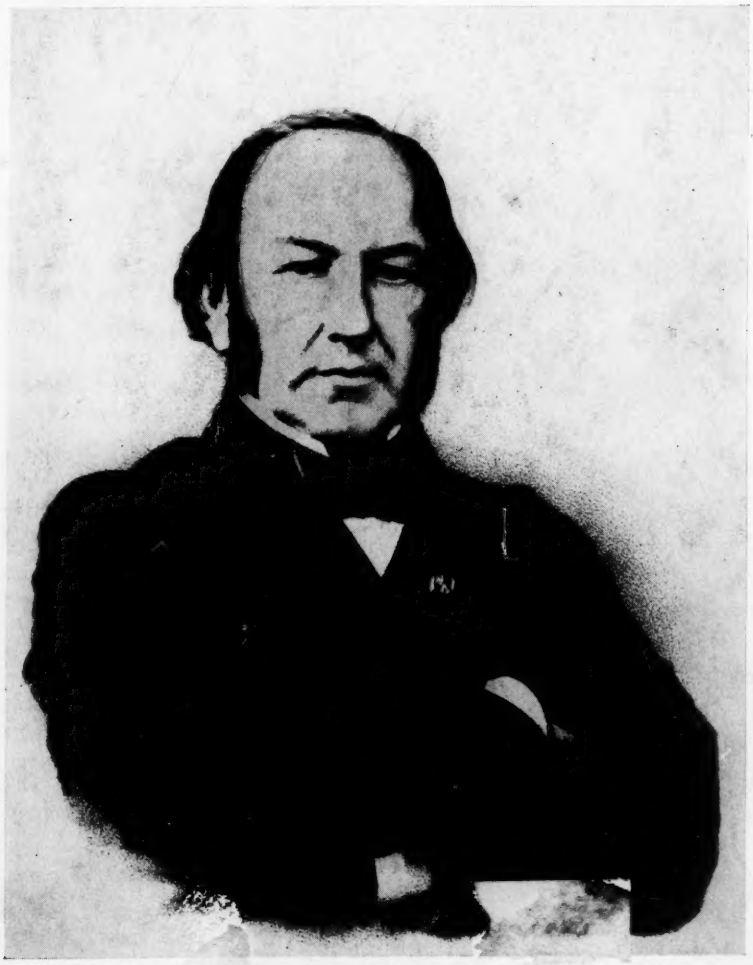

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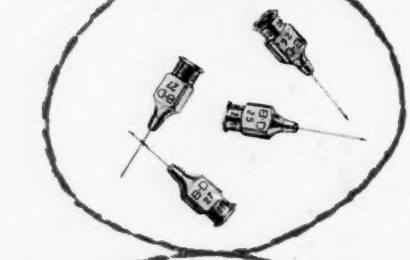

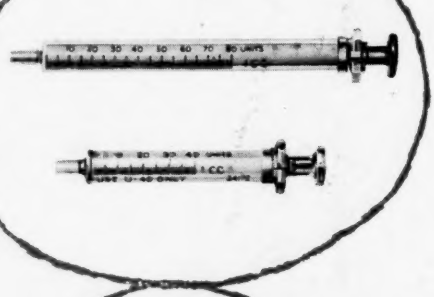

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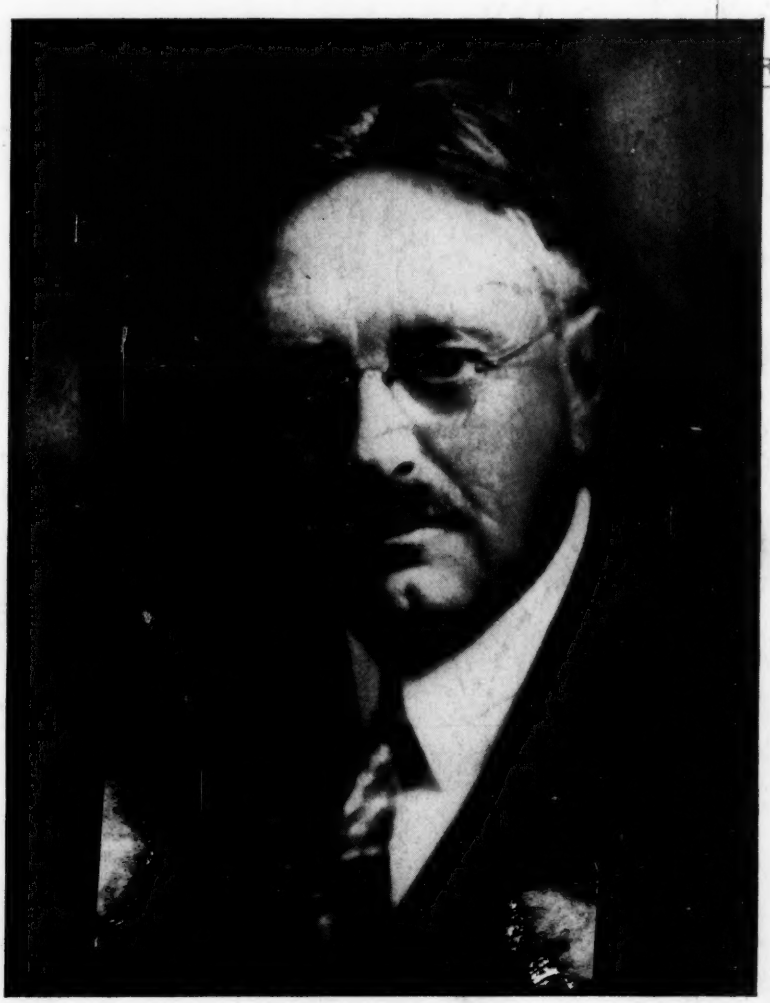

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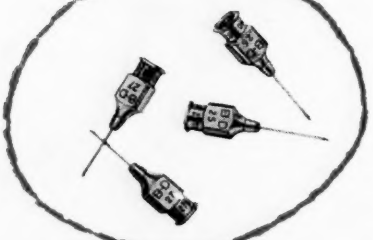

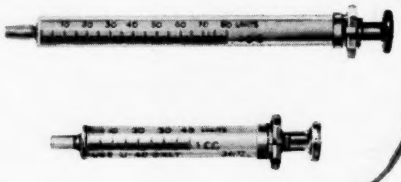

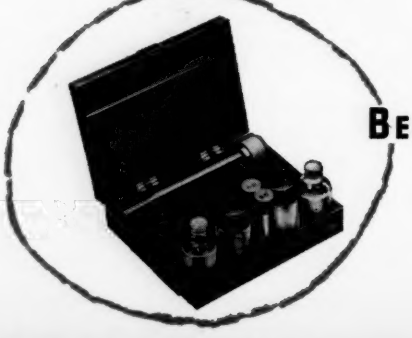

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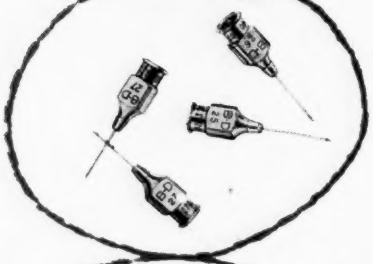

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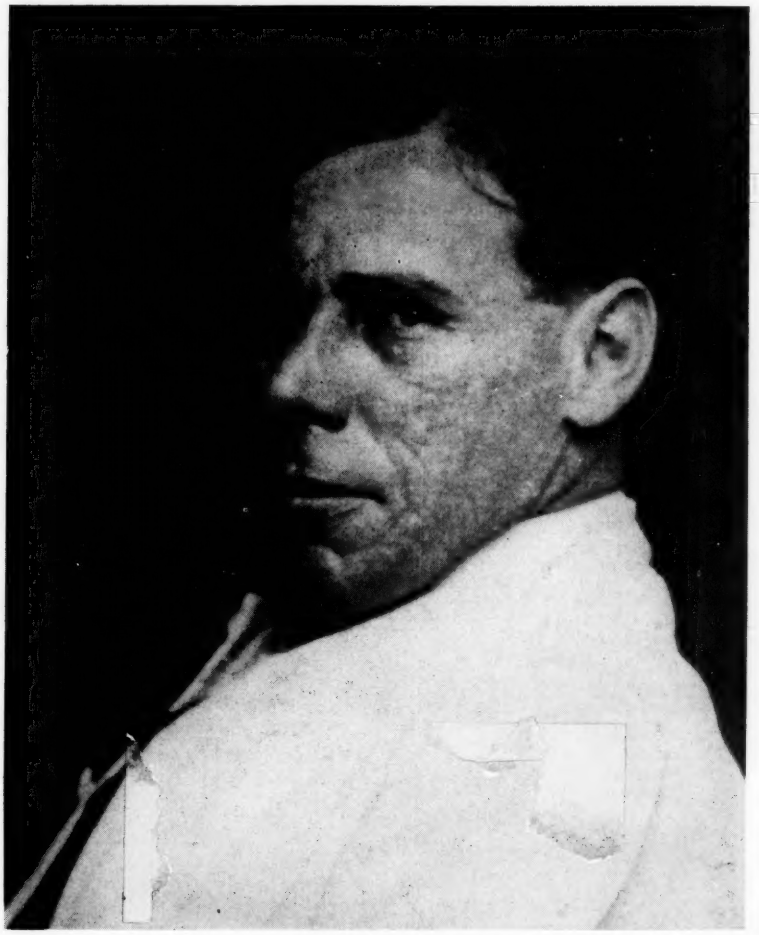

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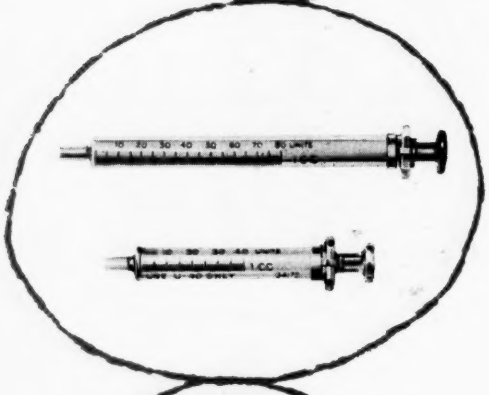

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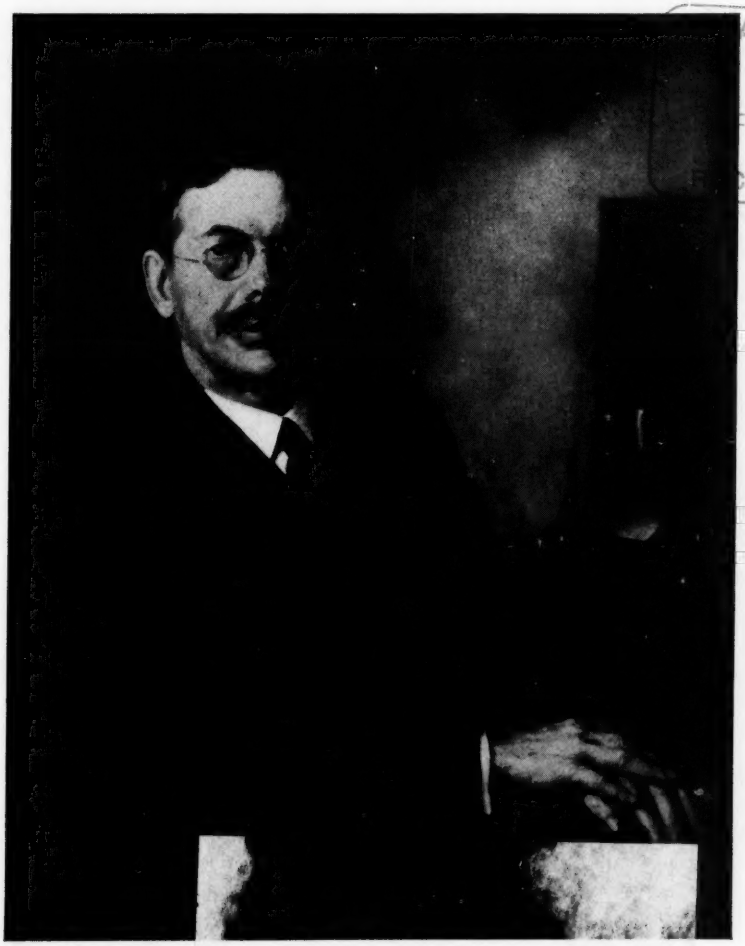

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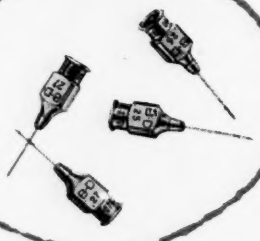

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